Regulatory factors in ontogeny I.

Transcription factors and Hox genes

Developmental Biology I.

2019/20/1

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Central question of developmental biology:

How will linear genetic information stored in DNA help to become a three-dimensional adult organism?

Different cell types make different sets of proteins, even through their genomes are identical. Each human beings has roughly 150000 genes in each nucleus, but each cell uses only a small subset of these genes. Moreover different cell types use different subsets of these genes. Developmental genetics is the discipline that examines how the genotype is transformed into the phenotype, and the major paradigm of developmental genetics is differential gene expression from the same nuclear repertoire.

↓

During the differentiation of different cell types
there is no irreversible structural change of the genome,
but the gene expression pattern changes
(differential gene expression).
[except immune cells]

What determines the particular pattern of gene activity in a differentiated cell?

The regulationof gene expression can be accomplished at several levels:

- Differential gene transcription
- Selective nuclear RNA processing
- Selective mRNA translation
- Posttranslational modification of the proteins

Levels of gene expression in Eukaryotes

Transcription

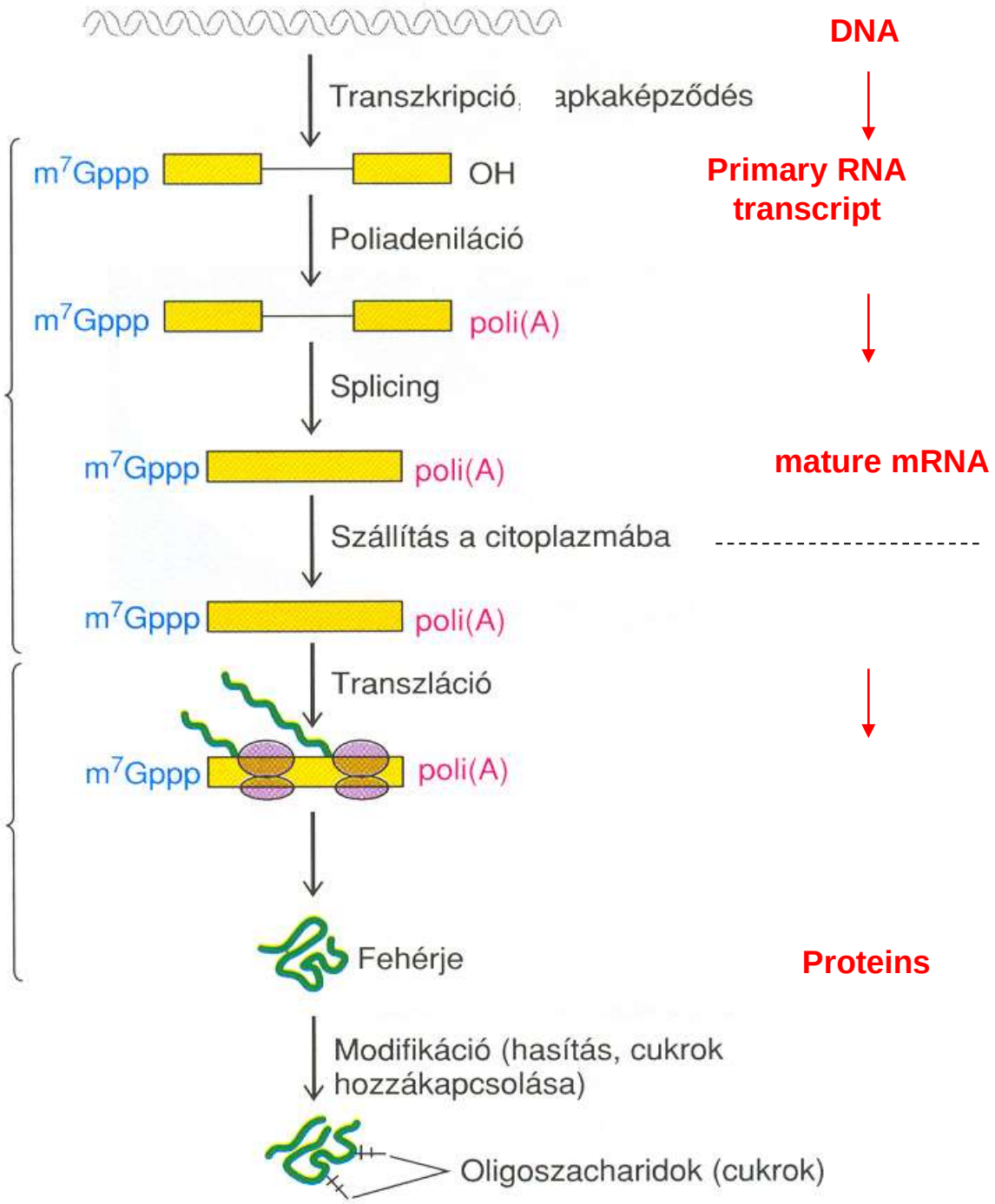
Nucleus

Posttranscription

Cytoplasm

Translation

Posttranslation



Transcription and translation are separated in time and space – it enhances the complexity of eukaryotic gene expression.

Different levels of gene expression regulation

1. Transcription ON / OFF
2. Intensity of transcription
3. mRNA maturation and stability (Eukaryotes)
4. Intensity of translation
5. Protein modification (posttranslational)
6. Protein lifetime regulation (ubiquitin/proteosome system, autophagy)

Regulation of gene expression: transcriptional level

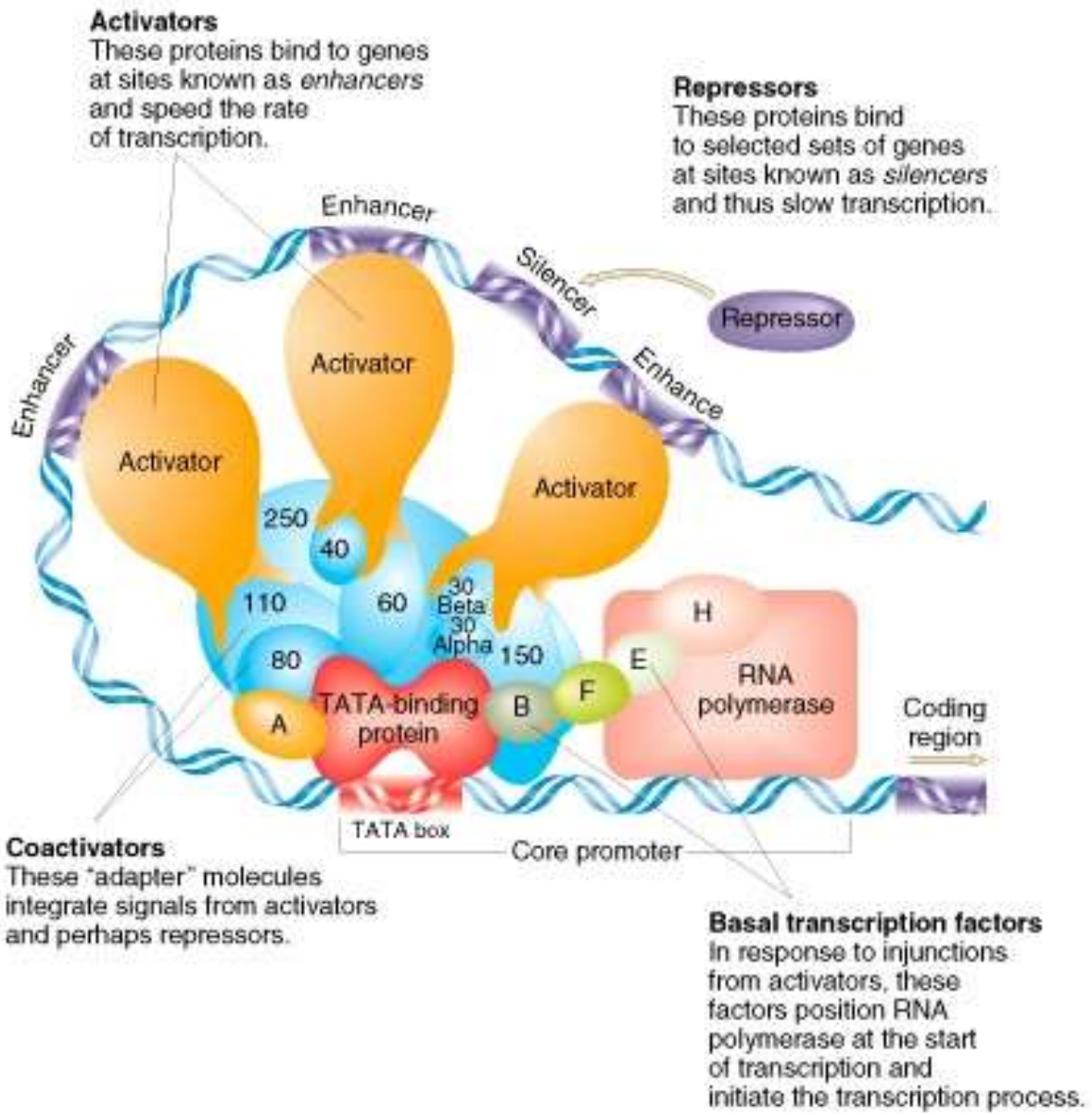
In every cell at given time only a set of genes function, the other genes are silenced. The cells need to have the following mechanisms to do this:

1. Mechanisms that turn the genes ON / OFF

2. this mechanism must recognize the circumstances that require the activation or inactivation of a gene

Role: during ontogeny (differentiation: some proteins appear, others block); in mature organism – adaptation to the environment, cell division, response to external signals …

Elements of transcription



The extent of gene expression is the result of the combined effect of all of these.

Regulation of eukaryotic gene expression at the transcriptional level

-Transcriptional regulation is carried out using so called ***cis*** and ***trans*** elements. *Cis* elements are specific DNA fragments located on the DNA strand where the gene of interest (whose expression is regulated by them) can be found. *Cis* elements serve as binding sites for *trans* elements. *Trans* elements are transcription factors or other factors regulating transcription (activators, co-activators, repressors), which bind to *cis* elements and can activate or repress transcription. Sequences encoding trans elements can be found anywhere in the genom (they are not necessarily located on the same DNA strand where the gene of interest can be found: origin of the nomenclature).

-*Cis-regulative* sequences: promoters, enhancers and insulators.
-*Trans* factors: transcription factors, activators, repressors.

-Studying the interaction of *cis* and *trans* elements: identifying DNA-protein interactions.

Transcription factors (*trans elements*) and regulatory (binding)sites (*cis elements*)

Cis regulatory elements: promoters, *enhancers*, *silencers* and *insulators* (DNA sequences)

Trans-acting elements: transcription factors (regulatory proteins acting on cis elements)

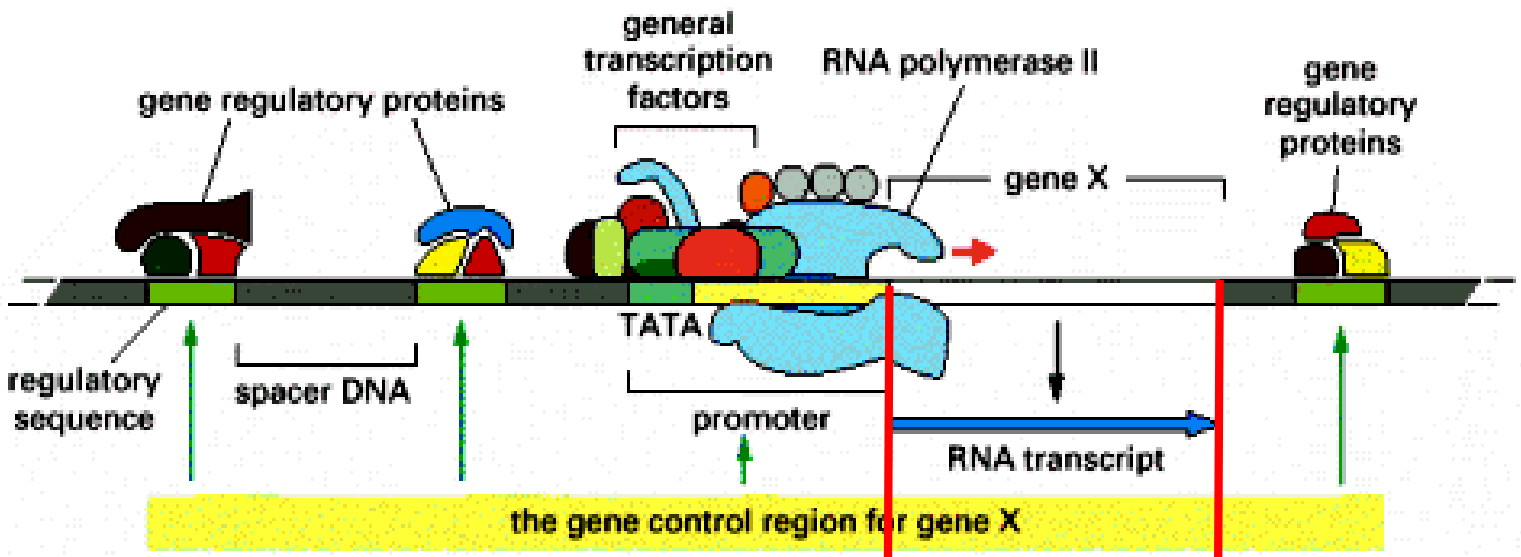
Differential gene expression

Every cell in the body carries the same genetic information, yet the organisms are made up of many different cell types. Tissue differentiation refers to the irreversible deactivation of some genes and the irreversible activation of others.

Eukaryotic genes can be divided into three groups:

- Housekeeping genes: expressed continuously in all cells (constitutive expression, e.g.cellular respiration)
- Genes specific to a given cell or tissue type (eg antibody production of plasma cells)
- Genes expressed only under certain conditions (eg, hormones regulated by hormones)

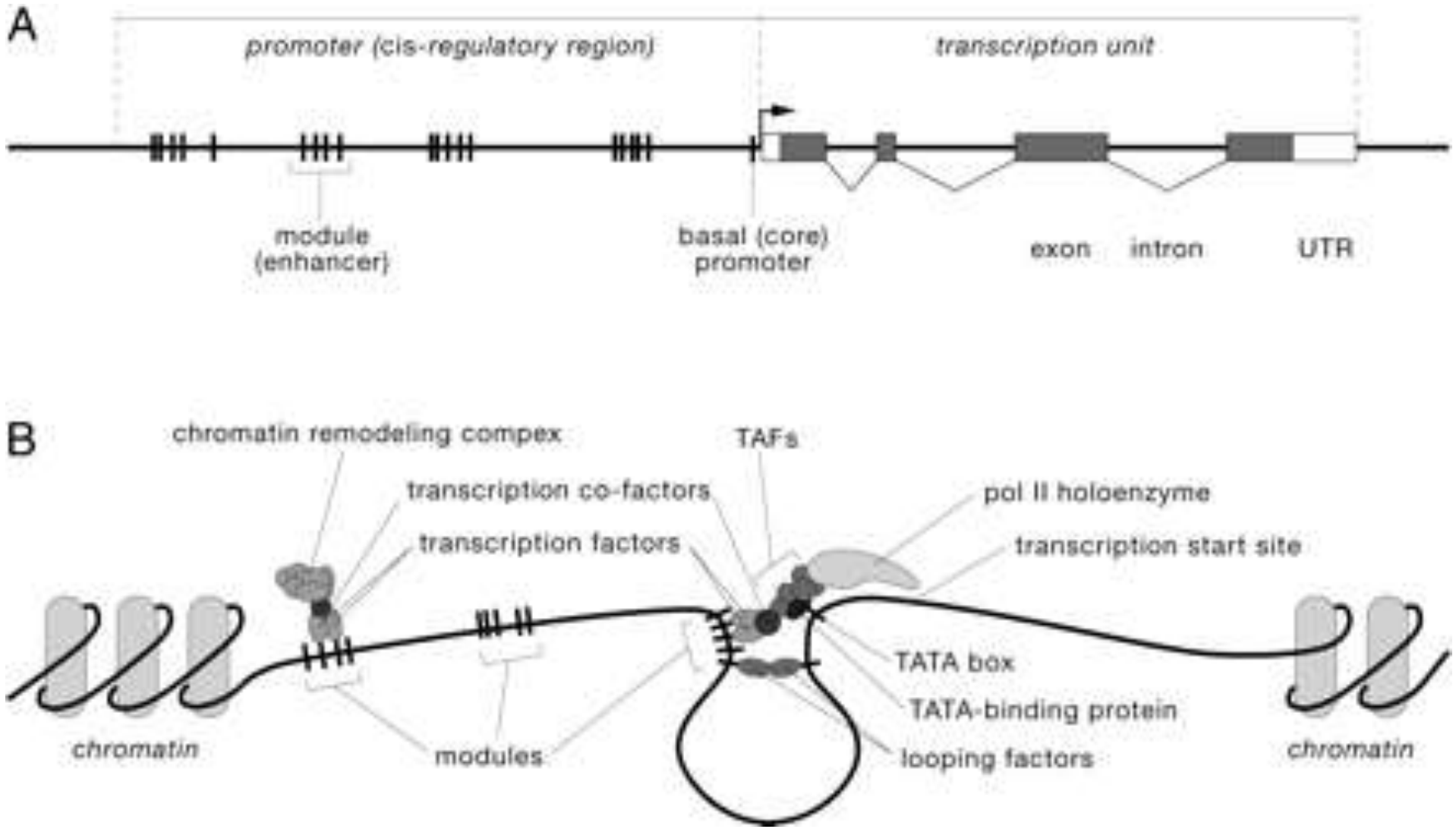
Eukaryotic genes in general



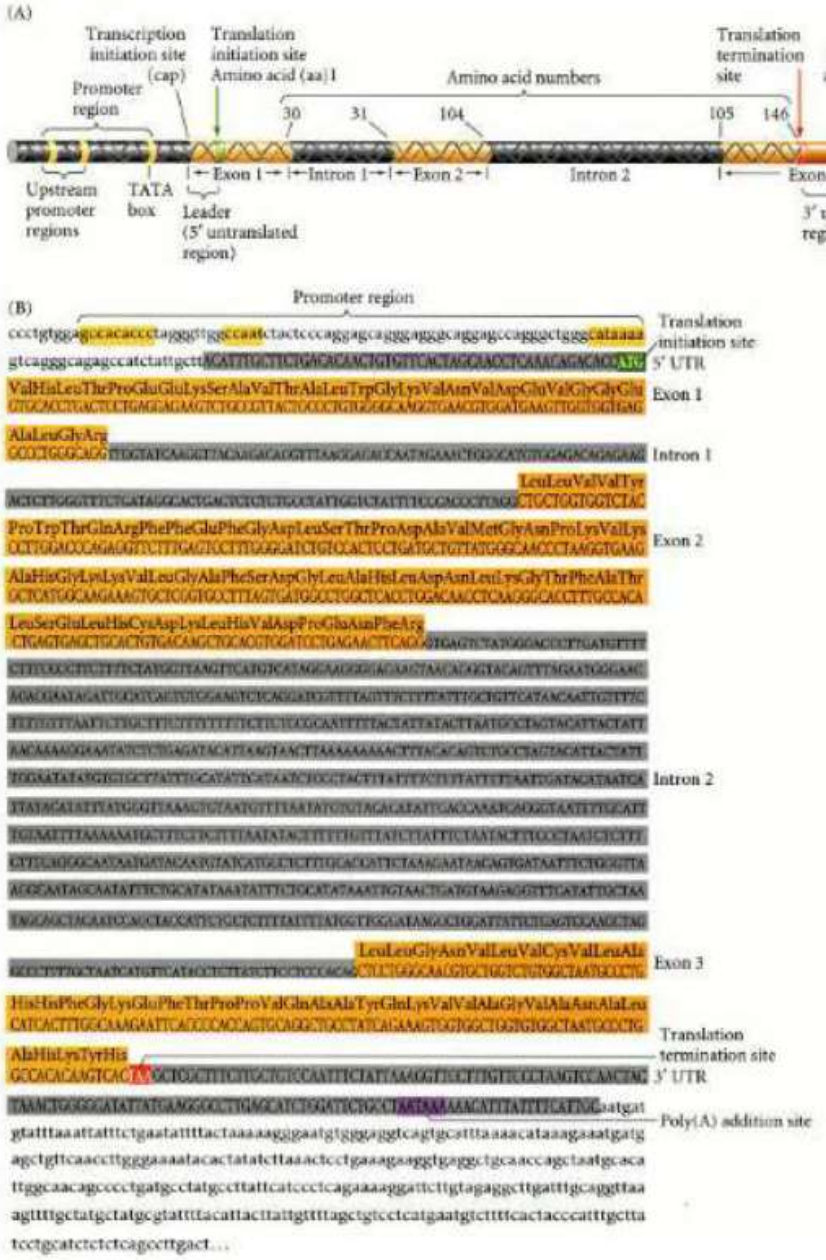
5’ regulatory region

Trans-criptional unit (exon+intron)

3’ regulatory region


A
promoter (cis-regulatory region)
transcription unit
module
(enhancer)
basal (core)
promoter
exon
intron
UTR
B
chromatin remodeling compex
TAFs
transcription co-factors
transcription factors
pol II holoenzyme
transcription start site
TATA box
TATA-binding protein
looping factors
chromatin
modules
chromatin

Anatomy of the eukaryotic genes: the human β-globin gene as an example



This gene consists of the following elements:

1. A promoter region, which is responsible for the binding of RNA polymerase and for the subsequent initiation of transcription. The promoter region of the human β-globingene has three distinct units andextends from 95 to 26 base pairs before ("upstream from") the transcription initiation site (i.e., from -95 to -26).

2. The transcription initiation site, which for human β-globin is ACATTTG. This site is often called the **cap sequence because it represents the 5′ end of the RNA, which will receive a "cap"**of modified nucleotides soon after it is transcribed. The specific cap sequence varies amonggenes.

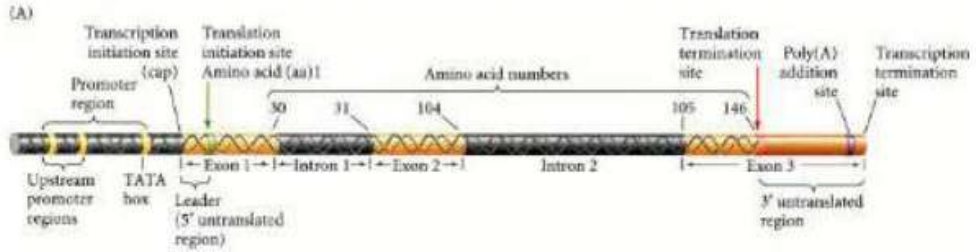
3. The translation initiation site, ATG. This codon (which becomes AUG in the mRNA) is located 50 base pairs after the transcription initiation site in the human β-globin gene (although this distance differs greatly among different genes). The intervening sequence of 50 base pairs between the initiation points of transcription and translation is the **5′ untranslated region, often** called the 5′ UTR or **leader sequence. The 5′ UTR can determine the rate at which translation is** initiated.

4. The first exon, which contains 90 base pairs coding for amino acids 1 30 of human β-globin.

5. An intron containing 130 base pairs with no coding sequences for the globin protein. The structure of this intron is important in enabling the RNA to be processed into messenger RNA and exit from the nucleus.

6. An exon containing 222 base pairs coding for amino acids 31 104.

Eukarióta „gén anatómia” a humán β-globin gén példáján 2.

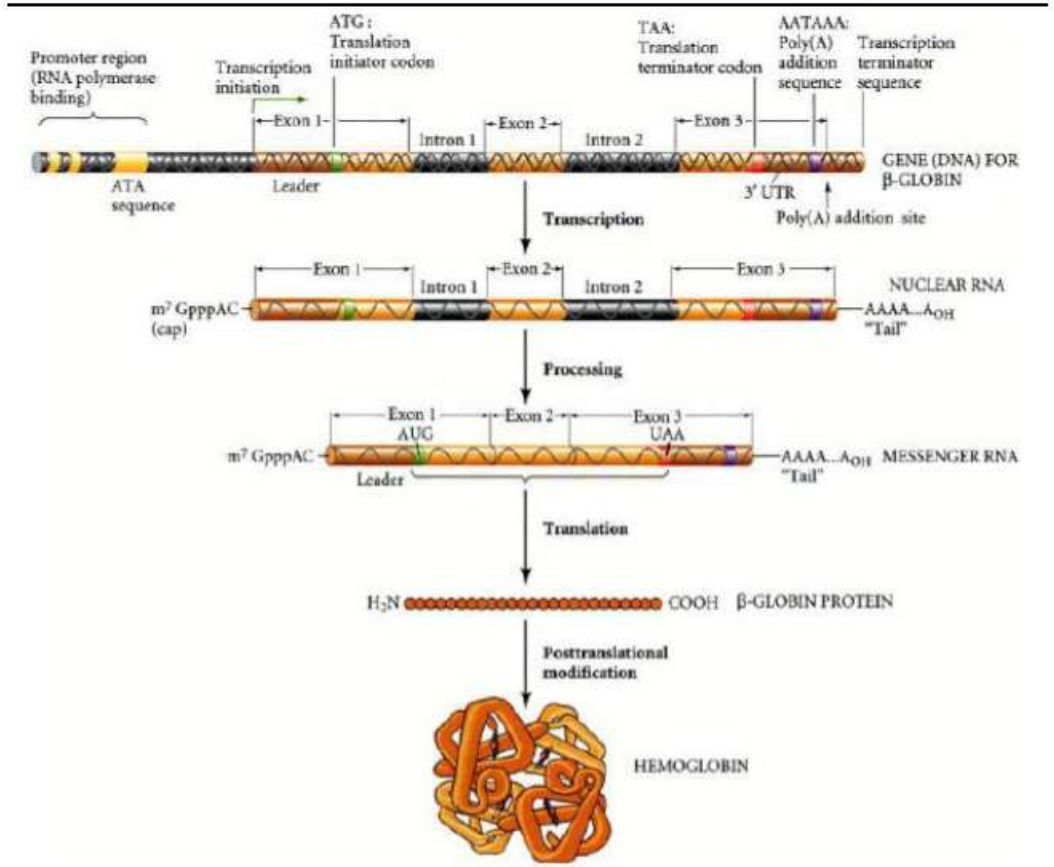


7. A large intron 850 base pairs having nothing to do with the globin protein structure.

8. An exon containing 126 base pairs coding for amino acids 105 146.

9. A translation termination codon, TAA. This codon becomes UAA in the mRNA. The ribosome dissociates at this codon, and the protein is released.

10. A 3′ untranslated region that, (3′ UTR) although transcribed, is not translated into protein.
This region includes the sequence AATAAA, which is needed for **polyadenylation: the lacement** of a "tail" of some 200 to 300 adenylate residues on the RNA transcript. This **poly(A) tail**
(1) confers stability on the mRNA, (2) allows the mRNA to exit the nucleus, and (3) permits the mRNA to be translated into protein. The poly(A) tail is inserted into the RNA about 20 bases downstream of the AAUAAA sequence. Transcription continues beyond the AATAAA site for about 1000 nucleotides before being terminated.

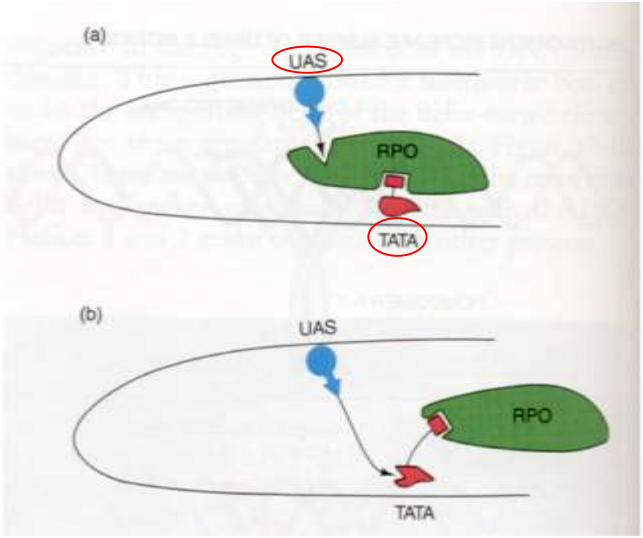


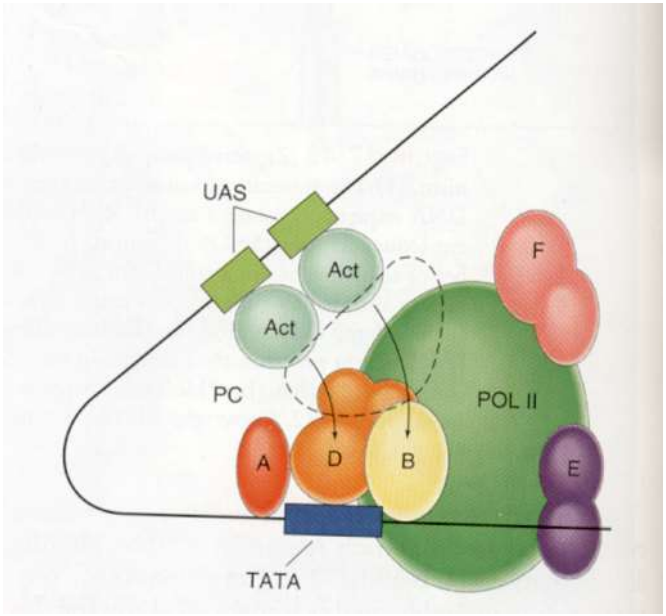
The original nuclear RNA transcript for such a gene contains the capping sequence, the 5′ untranslated region, the exons, the introns, and the 3′ untranslated region (Figure 5.3). In addition, both its ends become modified. A cap consisting of methylated guanosine is placed on the 5′ end of the RNA in opposite polarity to the RNA itself. This means that there is no free 5′ phosphate group on the nuclear RNA. The 5′ cap is necessary for the binding of mRNA to the ribosome and for subsequent translation (Shatkin 1976). The 3′ terminus is usually modified in the nucleus by the addition of a poly(A) tail. These adenylate residues are put together enzymatically and are added to the transcript; they are not part of the gene sequence. Both the 5′ and 3′ modifications may protect the RNA from exonucleases that would otherwise digest the mRNA (Sheiness and Darnell 1973; Gedamu and Dixon 1978). The modifications thus stabilize the message and its precursor.

Enhancers

- ***Cis*** elements, which increase the rate of transcription, switch on or off genes (repressing elements are called silencers).
- Enhancers can regulate the gene of interest even from big distances (many thousands of base pairs). Enhancers can be located upstream of the gene (5' regulatory region, promoter), in downstream regulatory regions (for example 3'UTR) and also in introns.
- Enhancers are key elements of differential transcription: activate or repress genes functioning in a given cell type (tissue), at the given time point of development, thus they **ensure specificity in time and space**.
- A gene has generally more enhancers and different transcription factors might bind to each enhancer. Different enhancers can activate the given gene in different cell types and/or in different developmental stages.
- Enhancers are modular. An enhancer modul consists of different DNA elements, whose variations build new moduls.

Enhancer sequences communicate with the BTA (basal transcriptional apparatus) through DNA-looping: enhancers exert their positive or negative effect on transcription this way.

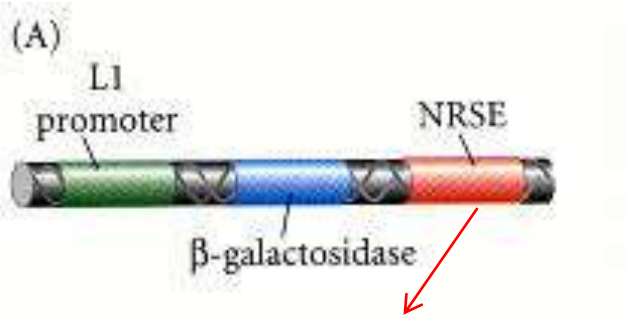




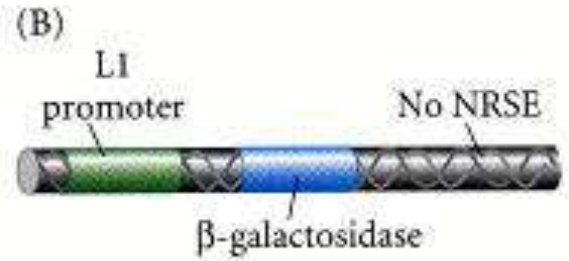
Silencers

Transcriptional inhibitors

Cis regulatory elements. Like the enhancers, they act on the same chromosome where the regulated gene (promoter) is. They inhibit the transcriptional activity.



(reduced expression - normal)



(ectopic expression - abnormal)

***NRSE*: neuron-restrictive silencer element**

Insulators

- **Insulators: genomic sequences, which are able to block promoter-enhancer or enhancer-enhancer interactions.**
- Enhancers and silencers can act to the gene expression from several kilobasepair distance.
- Insulator sequences are several 10 basepair long DNA, what lies between enhancer and promoter or silencer and promoter elements.
- Function: inhibiting the effect of enhancers or silencers of a given gene to other genes

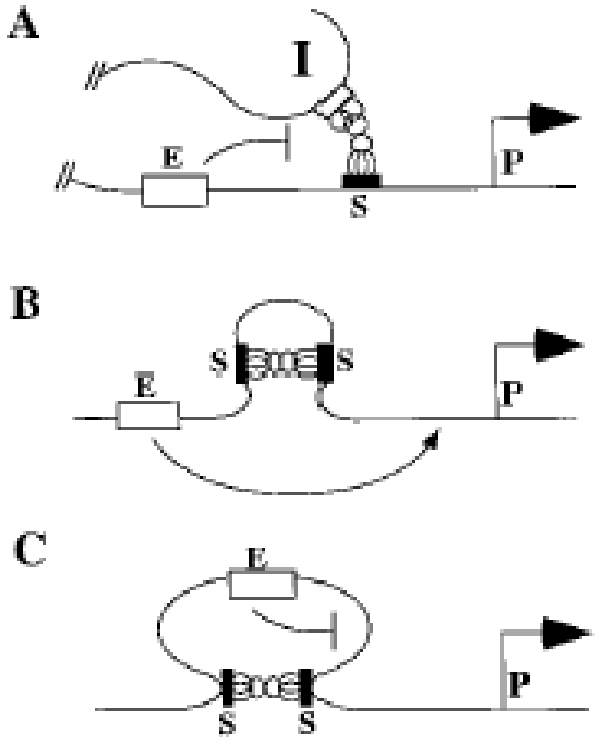
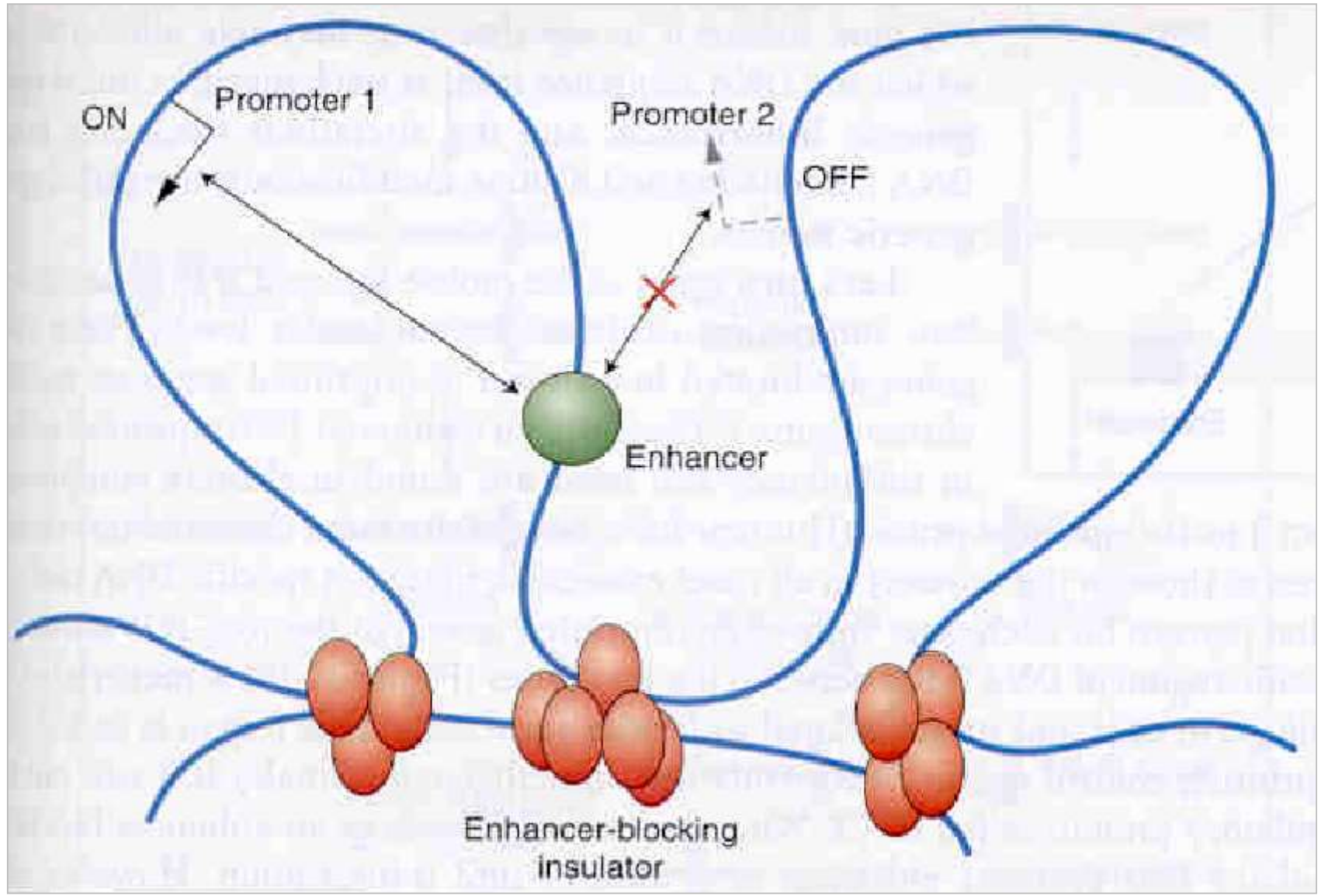


Fig. 4. Insulator-mediated loop formation. (A) A suHw insulator (S) may interact with other nuclear sites/insulators (I), separating the enhancer (E) and the promoter (P) into distinct domains and blocking their interaction. (B) Interactions between two tandem suHw insulators fail to sequester the enhancer and may even facilitate enhancer-promoter interaction by "looping out" the intervening DNA. (C) Enhancer blocking may be strengthened by the preferred interactions between two suHw insulators flanking the enhancer.

Enhancer blocking insulators form new DNA loops, which physically separate enhancers from promoters



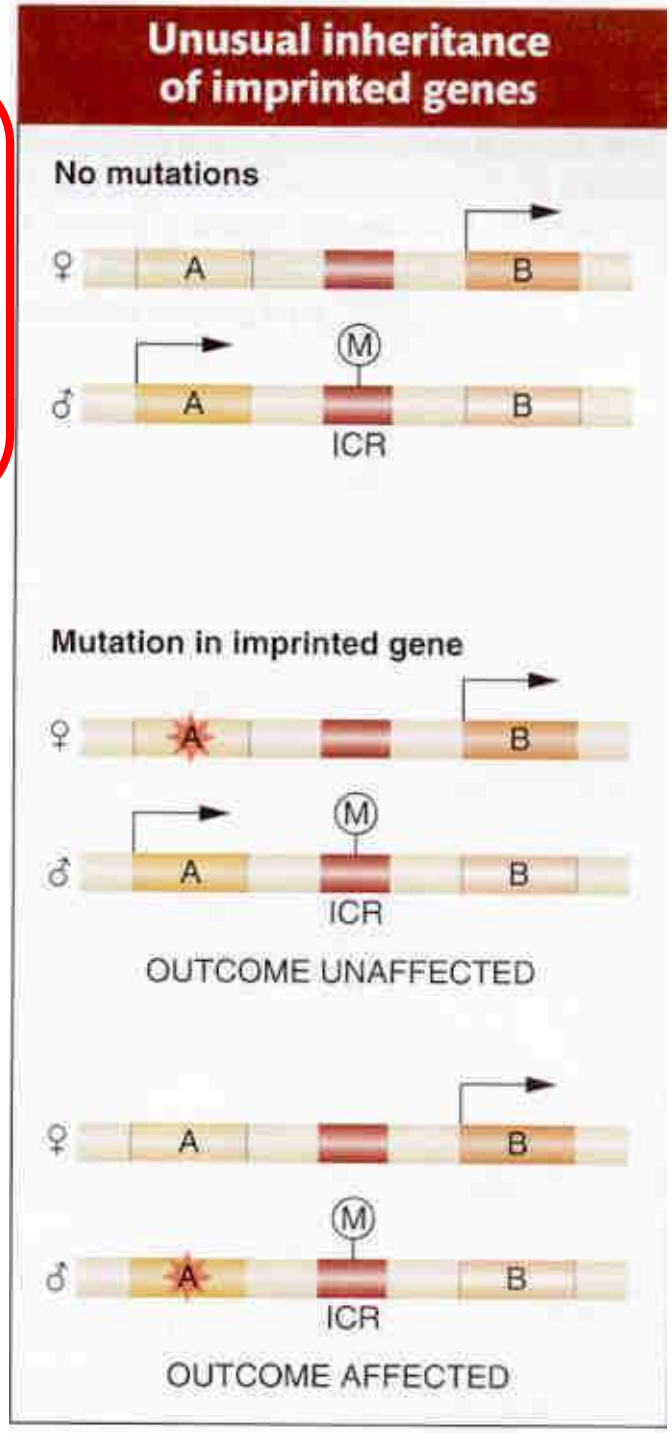
Genomic imprinting: an allele derived from one of the parents is inactive in case of autosomal genes.
Maternal imprinting: maternal allele is inactive, paternal allele is functioning.
Paternal imprinting: paternal allele is inactive, maternal allele is functioning. + examples

Imprinted autosomal genes show monoallelic inheritance.

Gene A results only a mutant phenotype if the paternal copy carries a mutation.

However, in the coding region of imprinted genes (such as mouse Igf2 és Igf2R gene) there was no mutation observed.
Imprinting is caused by sex-specific methylation of the promoter region of given alleles.

M: methylated promoter
ICR: imprinting control region



Imprinting in case of mouse Igf2 and Igf2R genes

Igf2 (Chr. 7): maternal imprinting, only the paternal allele is active.
Igf2R (Chr. 17): paternal imprinting, only the maternal allele is active.

Deletion occuring in the paternal Igf2R allele has no consequence.
In contrast, deletion in the maternal Igf2R allele is lethal, because no receptor is produced, which could bind the Igf2 ligand in excess. Dead embryos carrying an Igf2R deletion are about 30% bigger compared to wild-type embryos and show lysosomal defects.

Genomic environment of the Igf2 (Chr. 7) gene was examined in details in order to understand genomic imprinting:

ICR (imprinting control region) is not methylated on the maternal allele, therefore can bind to CTCF insulator. CTCF insulator inhibits the interaction of the Igf2 promoter and the 3' Igf2 enhancer, thus the maternal copy will be inactive.

ICR is methylated on the paternal allele, CTCF cannot bind to it, the 3' enhancer is able to regulate Igf2, therefore Igf2 is transcribed.

!!!

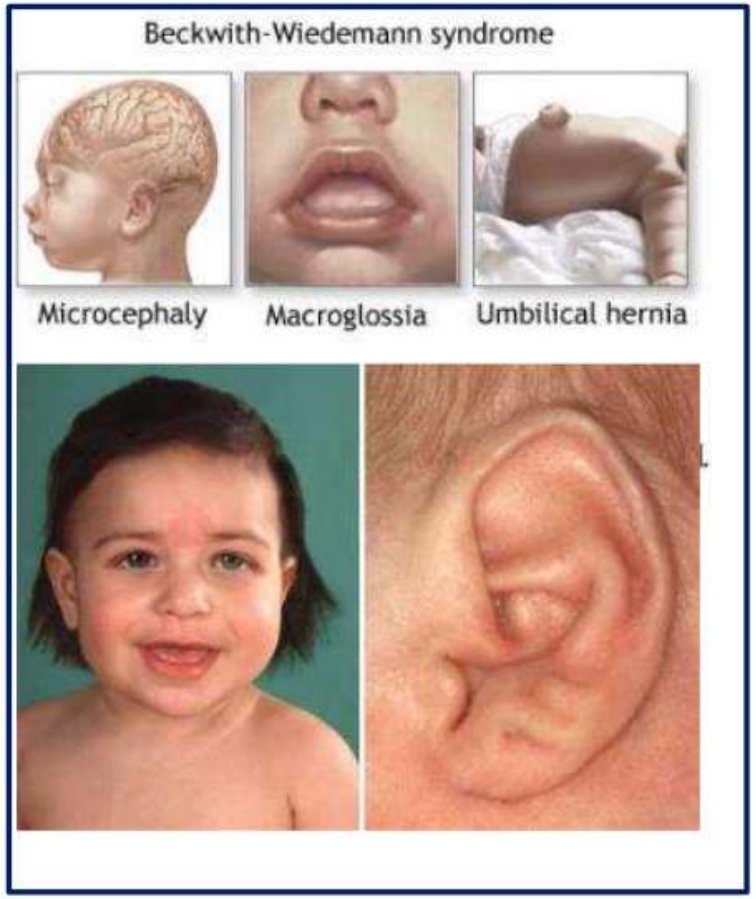
Conditions and Syndromes Associated with Parental Imprinting

Several other syndromes are also based on parental imprinting.

Beckwith-Wiedemann syndrome, characterized by fetal overgrowth and an increased incidence of childhood cancers, has been mapped to the imprinted region on chromosome 11, which contains the genes for insulinlike growth factor-II (IGF-II, which promotes cell proliferation) and H19 (a growth suppressor). It occurs when both alleles of the *IGF-2* gene express a paternal imprinting pattern.

Another instructive example involves deletion of the long arm of chromosome 15. Children of either sex who inherit the maternal deletion develop **Angelman's syndrome**, which includes severe mental retardation, seizures, and ataxia.

A child who inherits a paternal deletion of the same region develops **Prader-Willi syndrome**, characterized by obesity, short stature, hypogonadism, a bowed upper lip, and mild mental retardation.



Transcription factors

Transcription factors are specific proteins what can bind to regulatory regions of genes and activate or repress gene activity.

They can alter RNA synthesis by the following:

- Stabilizing the RNA polymerase binding to DNA
- Disrupting the nucleosome structure
- Increasing the efficiency of transcription

Trans elements: transcription factors

Transcription factors have three major domains:

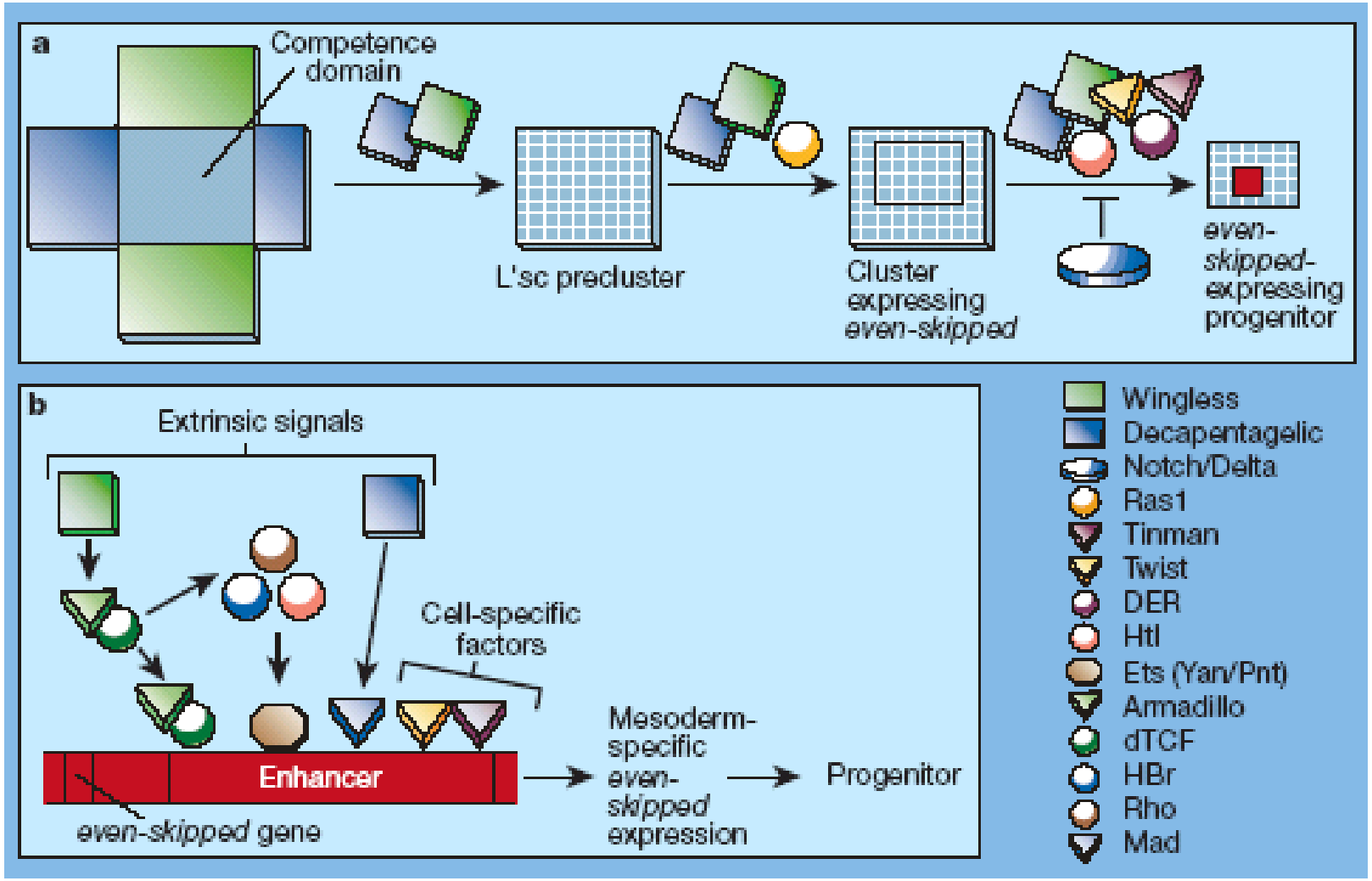
- DNA-binding domain: recognizes a particular DNA sequence
- Trans-activating domain: activates or supresses the transcription of the gene whose promoter or enhancer it has bound
- Protein-protein interaction domain: allows the transcription factor's activity to be modulated by other regulatory proteins

All transcription factor contains DNA-binding and protein-binding domain.

Gene activity depends on:

- TF concentation,
- TF quality (phosphorylated or not)
- and TF combinations.

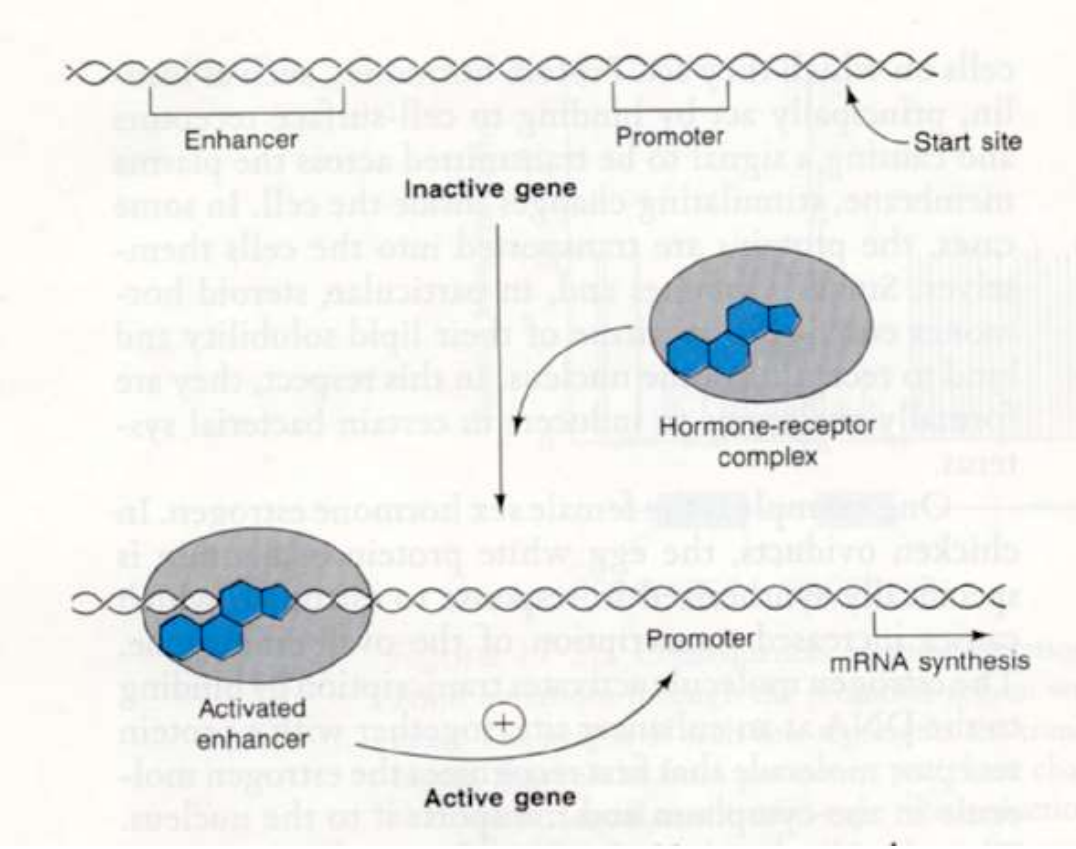
An example of combinatorial regulation: *Drosophila eve* enhancer



***eve* 3' enhancer integrates different signals resulting in specification of the heart muscle progenitor cell.**

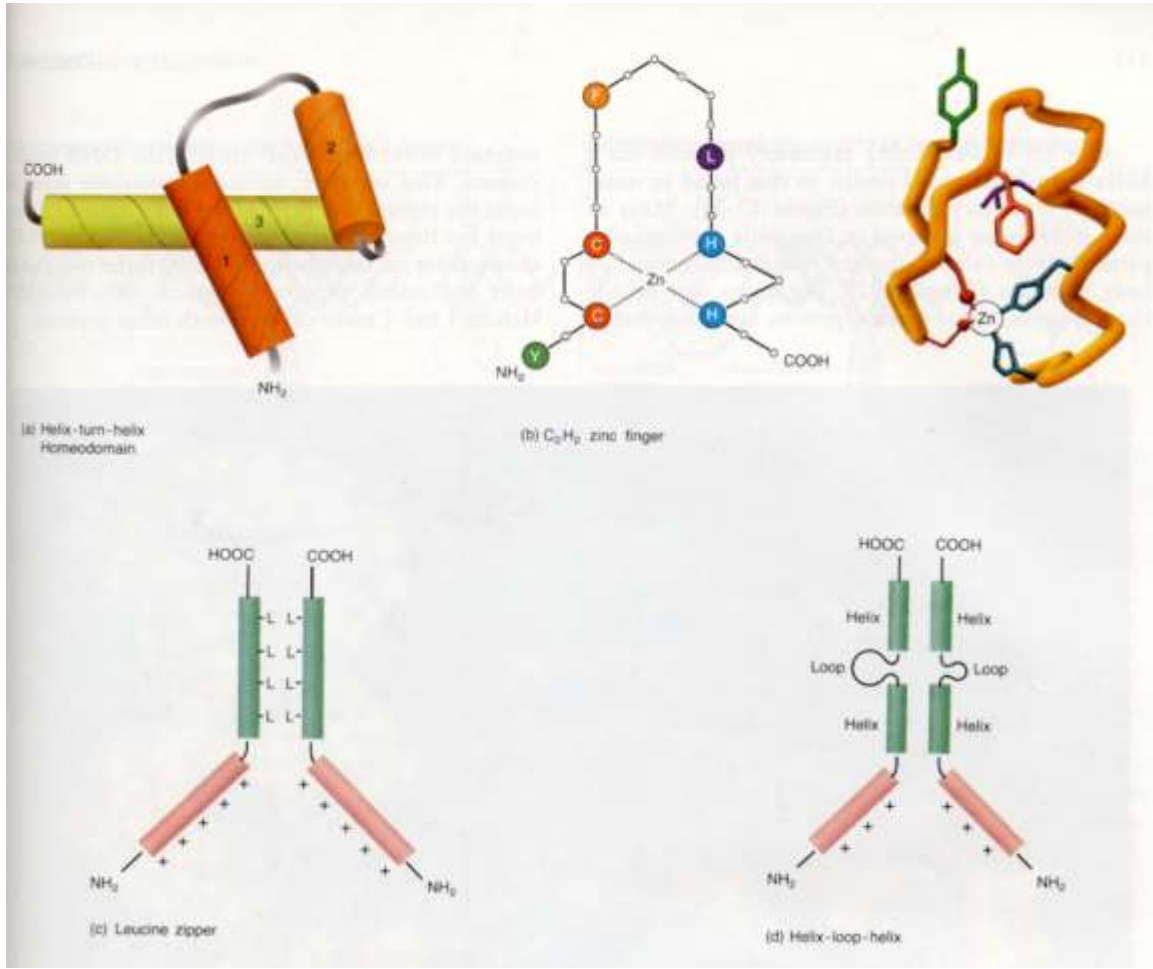
Steroid hormon/receptor complexes as special cases of *trans* factors

Steroid hormons- due to their structure – are able to get through the cell membrane then in the cytoplasm they join their receptor. The hormon-receptor complex is translocated to the nucleus, then it binds to enhancer sequences of given genes and regulates their transcription (from certain perspective hormons are analoguous to prokaryotic inducers). This is how the transcription of ovalbumin (the gene of egg white) is activated in the chicken oviduct: transcription of ovalbumin is induced by the oestrogen/oestrogen receptor.



Transcription factors are categorized based on their DNA-binding domain

- Helix-turn-helix, HTH
- Zinc-finger
- Leucin-zipper
- Helix-loop-helix, HLH



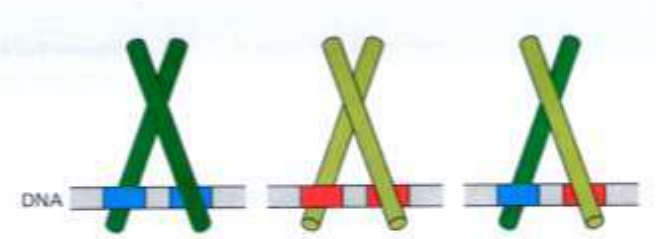
Leucine-zipper motif

-the dimeric Y shaped protein contains two extended a-helices that ”grip” the DNA, much like a pair of scissors at two adjacent major grooves separated by about half a turn of the double helix

-the motif contains the hydrophobic amino acid leucine at every seventh position in the sequence, they are

required for dimerisation

-C/EBP, AP1 (liver differentiation, fat cell specification)



Zinc finger

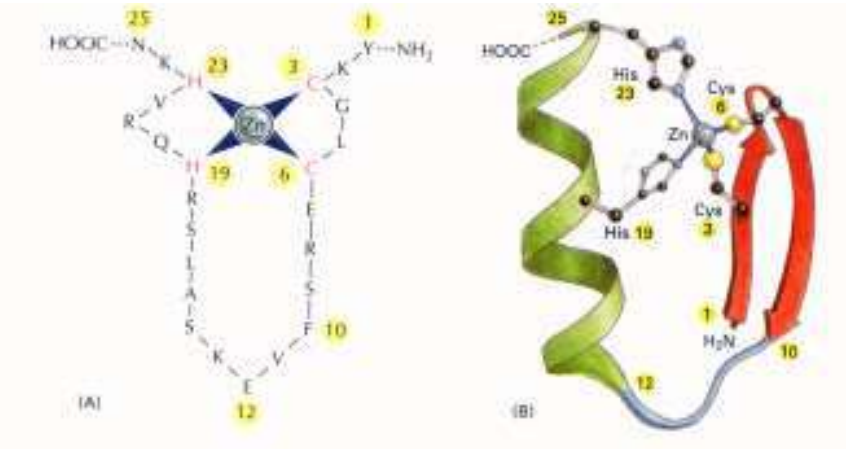
-number of different eukaryotic protein have regions that fold around a central Zn 2+ ion, producing a compact domain from a

relatively length of the polypeptide chain

-α-helix recognise the DNA

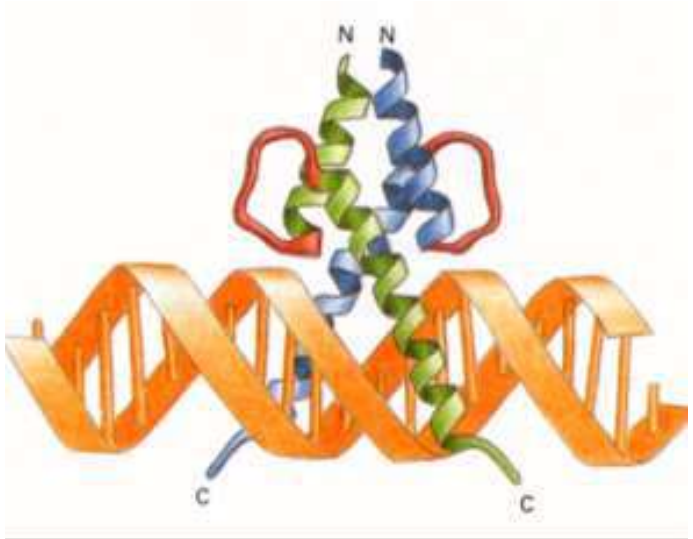
-WT1, Krüppel, Engrailed (kidney, gonad and macrophage development, Drosophila segmentation)

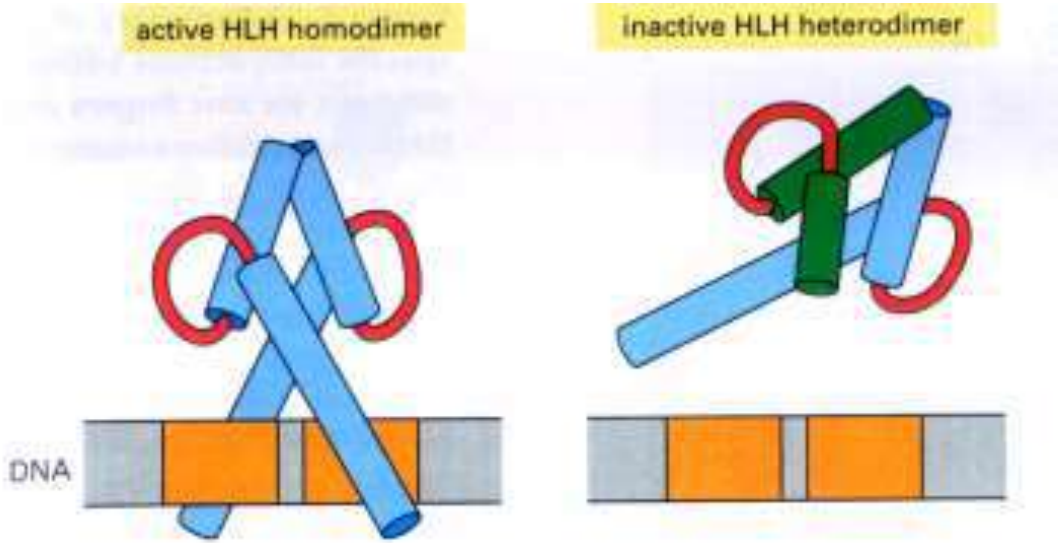
steroid receptors



Helix-loop-helix motif

Basic Helix-Loop-Helix (bHLH) Proteins The DNA-binding domain of another class of dimeric transcription factors contains a structural motif very similar to the basic-zipper motif except that a nonhelical loop of the polypeptide chain separates two α-helical regions in each monomer (Figure 11-22b). Termed a **basic helix-loop-helix (bHLH)**, this motif was predicted from the amino acid sequences of these proteins, which contain an N-terminal α helix with basic residues that interact with DNA, a middle loop region, and a C-terminal region with hydrophobic amino acids spaced at intervals characteristic of an amphipathic α helix. As with basic-zipper proteins, different bHLH proteins can form heterodimers.





Helix-turn-helix, HTH

-is present in many bacterial repressor protein

-dimerisation

-homeobox, POU (Oct genes, Pit1),

paired (Drosoph. paired, Pax genes),

winged HTH (c-ets, PU.1)

-two α-helices, one of them is called recognition helix

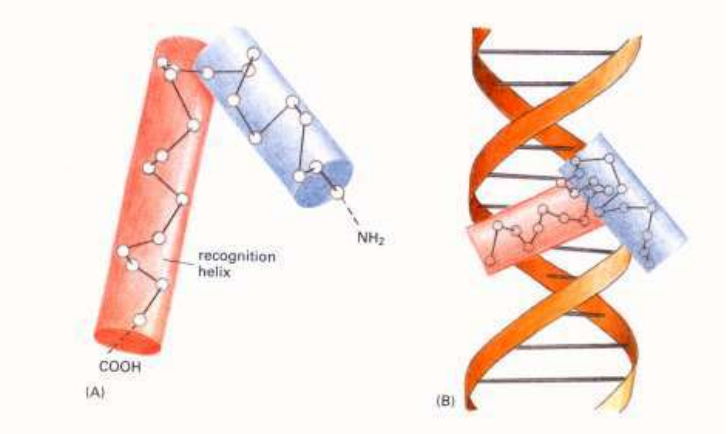
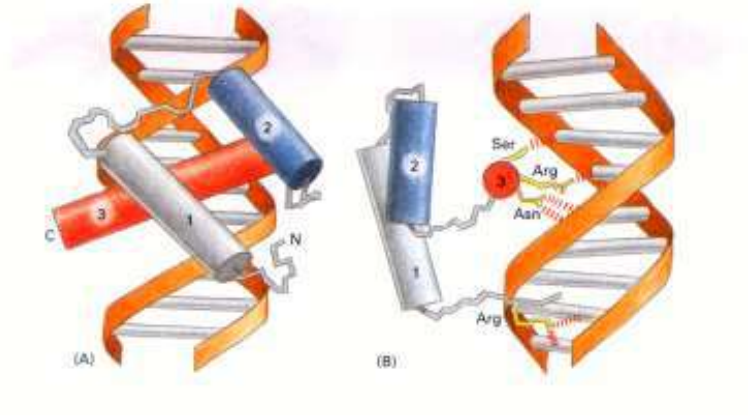


Table 5.1. Some major transcription factor families and subfamilies

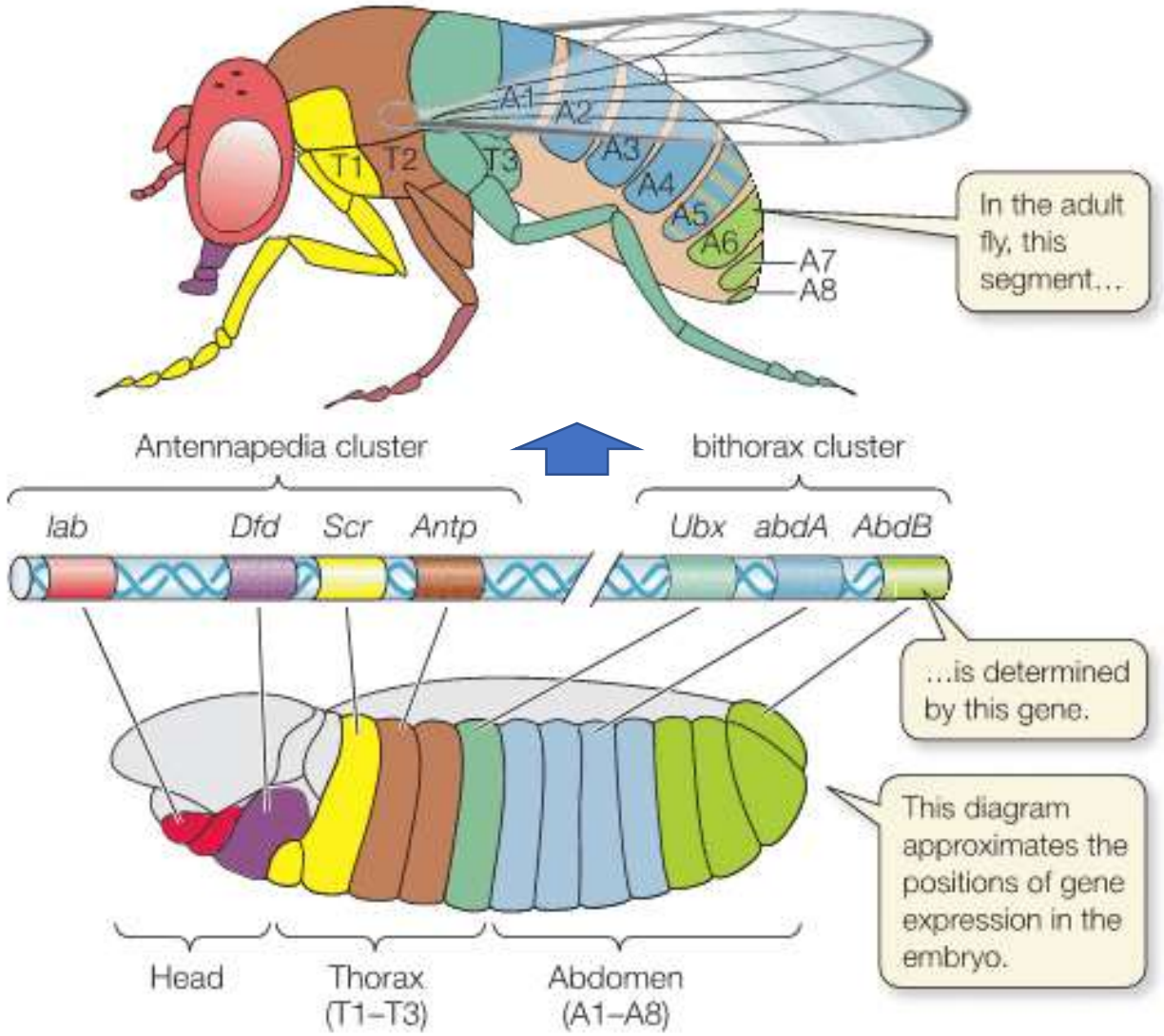
Family	Representative transcription factors	Some functions
Homeodomain:		
Hox	Hoxa-1, Hoxb-2, etc.	Axis formation
POU	Pit-1, Unc-86, Oct-2	Pituitary development; neural fate
LIM	Lim-1, Forkhead	Head development
Pax	Pax1, 2, 3, etc.	Neural specification; eye development
Basic helix-loop-helix (bHLH)	MyoD, achaete, daughterless	Muscle and nerve specification; *Drosophila* sex determination
Basic leucine zipper (bZip)	C/EBP, AP1	Liver differentiation; fat cell specification
Zinc finger:		
Standard	WT1, Krüppel, Engrailed	Kidney, gonad, and macrophage development; *Drosophila* segmentation
Nuclear hormone receptors	Glucocorticoid receptor, estrogen receptor, testosterone receptor, retinoic acid receptors	Secondary sex determination; craniofacial development; limb development
Sry-Sox	Sry, SoxD, Sox2	Bend DNA; mammalian primary sex determination; ectoderm differentiation

Homeobox gének

Many eukaryotic transcription factors that function during development contain a conserved 60-residue DNA-binding motif that is similar to the helix-turn-helix motif of bacterial repressors. Called **homeodomain proteins**, these transcription factors were first identified in *Drosophila* mutants in which one body part was transformed into another during development (Chapter 15). The conserved homeodomain sequence has also been found in vertebrate transcription factors, including those that have similar master control functions in human development.



Hox genes -
Master regulators of ontogeny

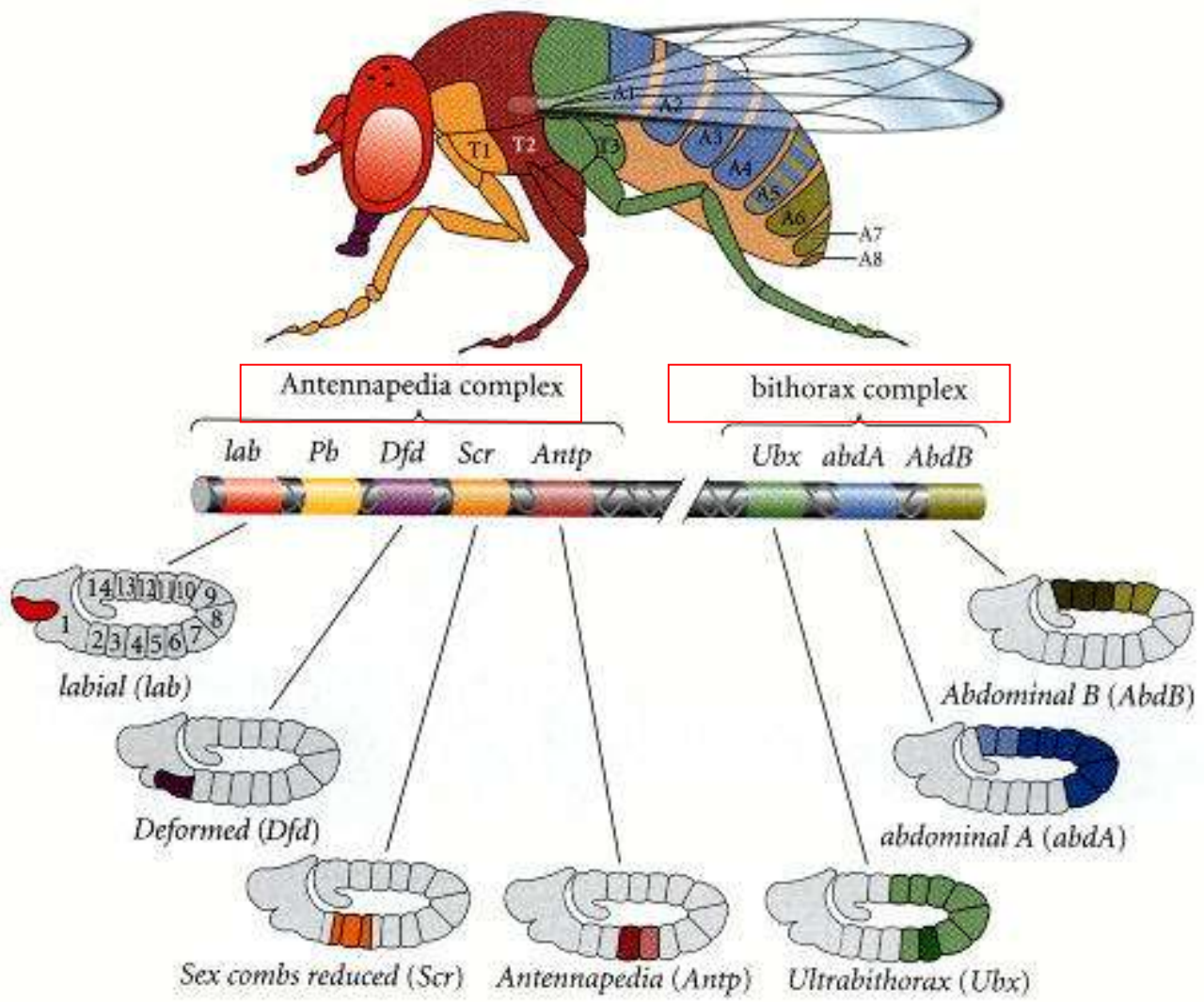


A subset of homeotic selector genes

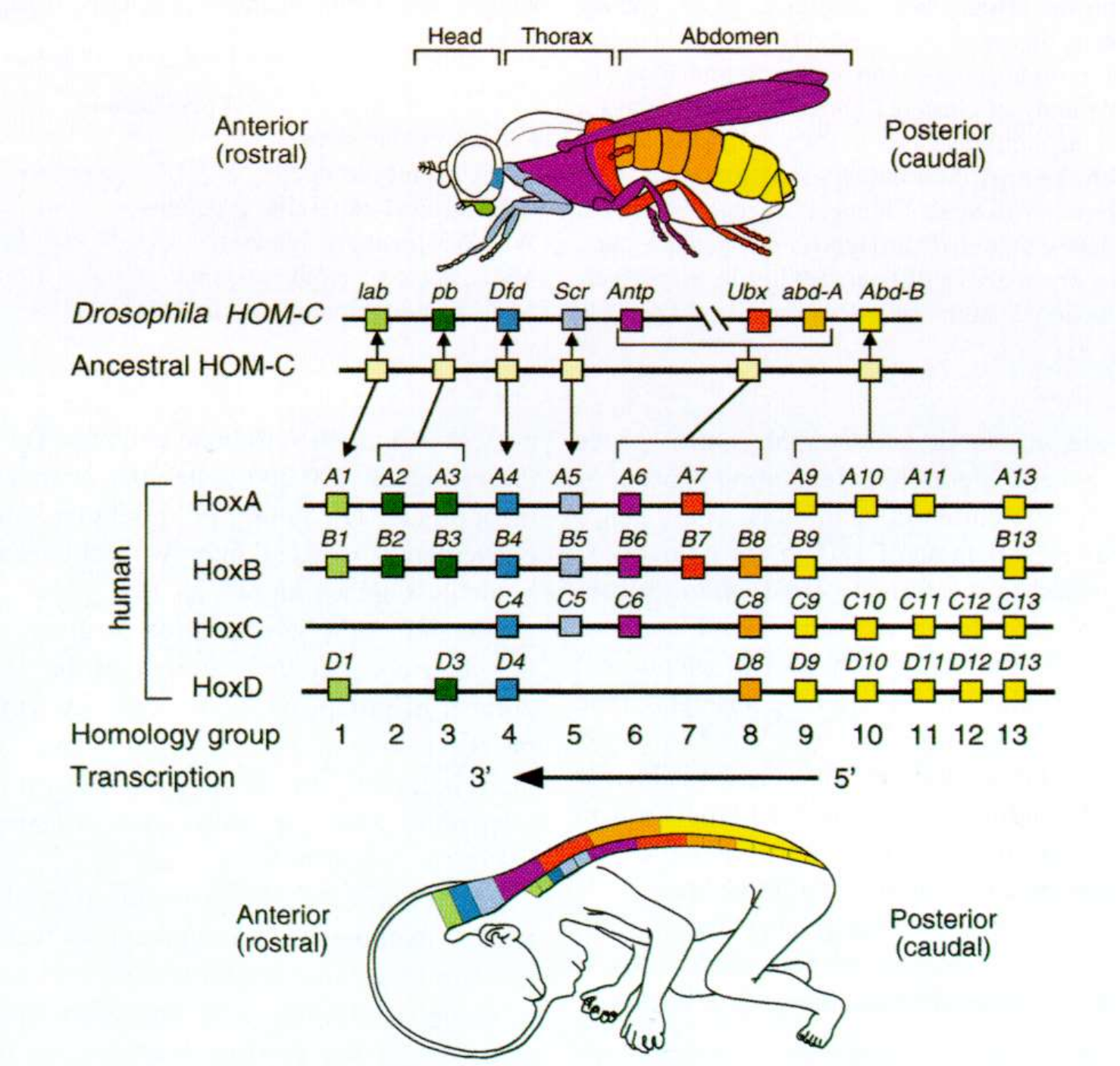
Clusters in the genome

Collinearity:
the position of the gene in the cluster coincides with the expression pattern in the body

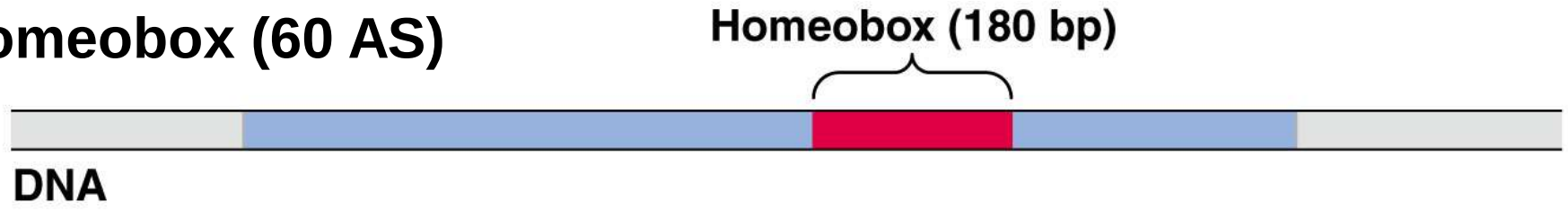
- **Coding transcription factor**
- **h*elix-turn-helix motif***
- **In clusters on chromosomes**



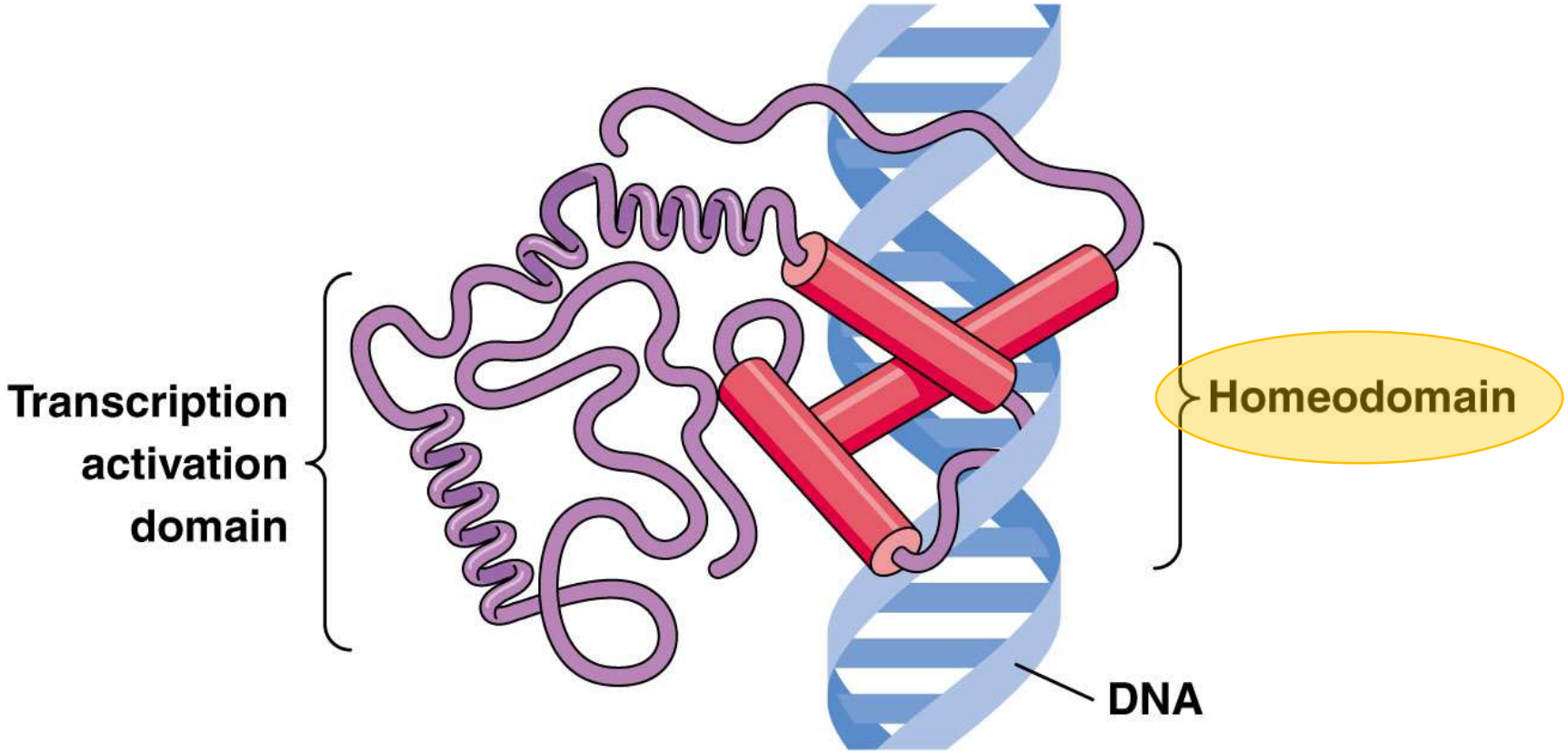
Cell fate determination along the anteroposterior body axis



Homeobox (60 AS)



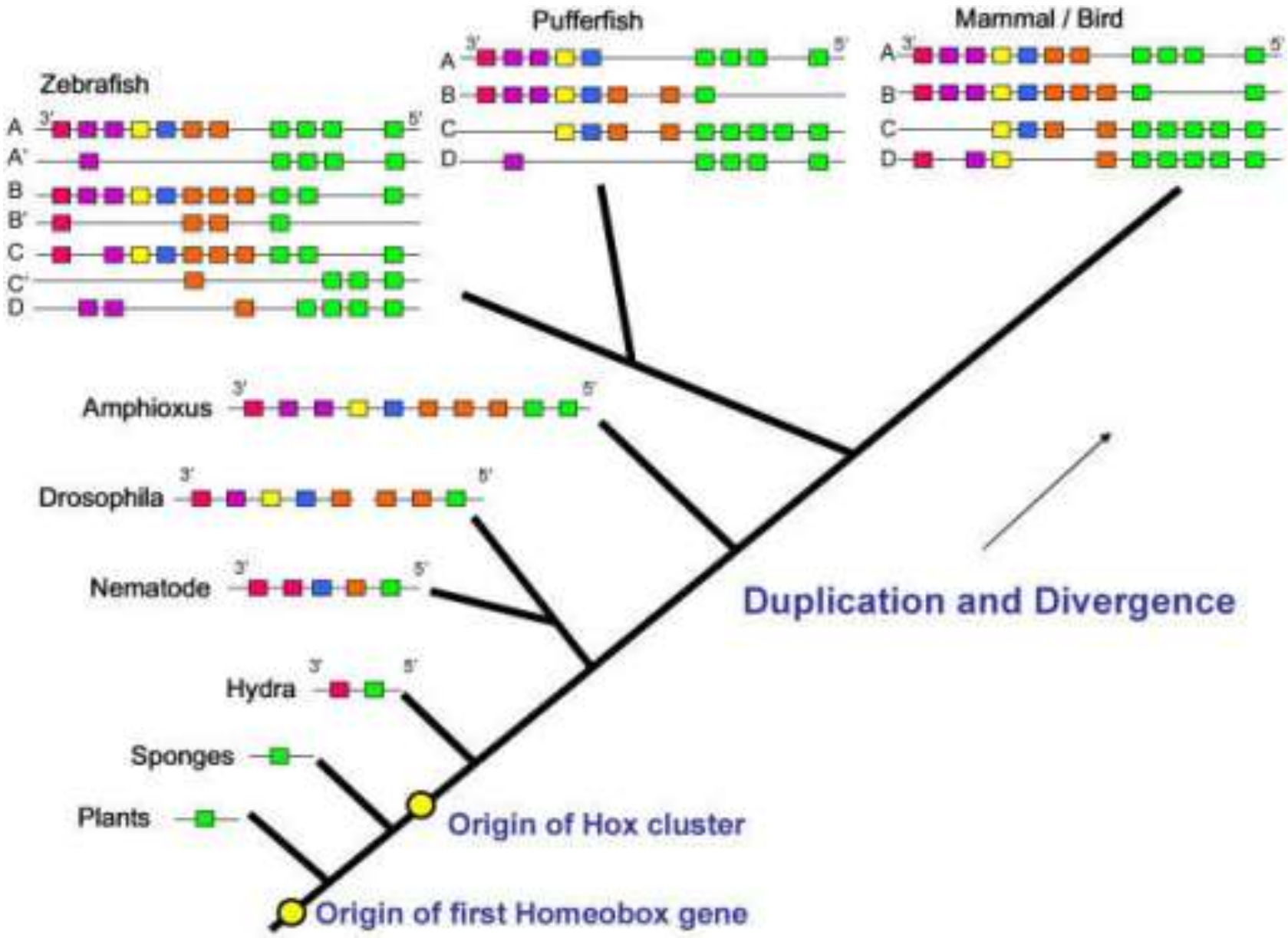
(a) Homeotic gene



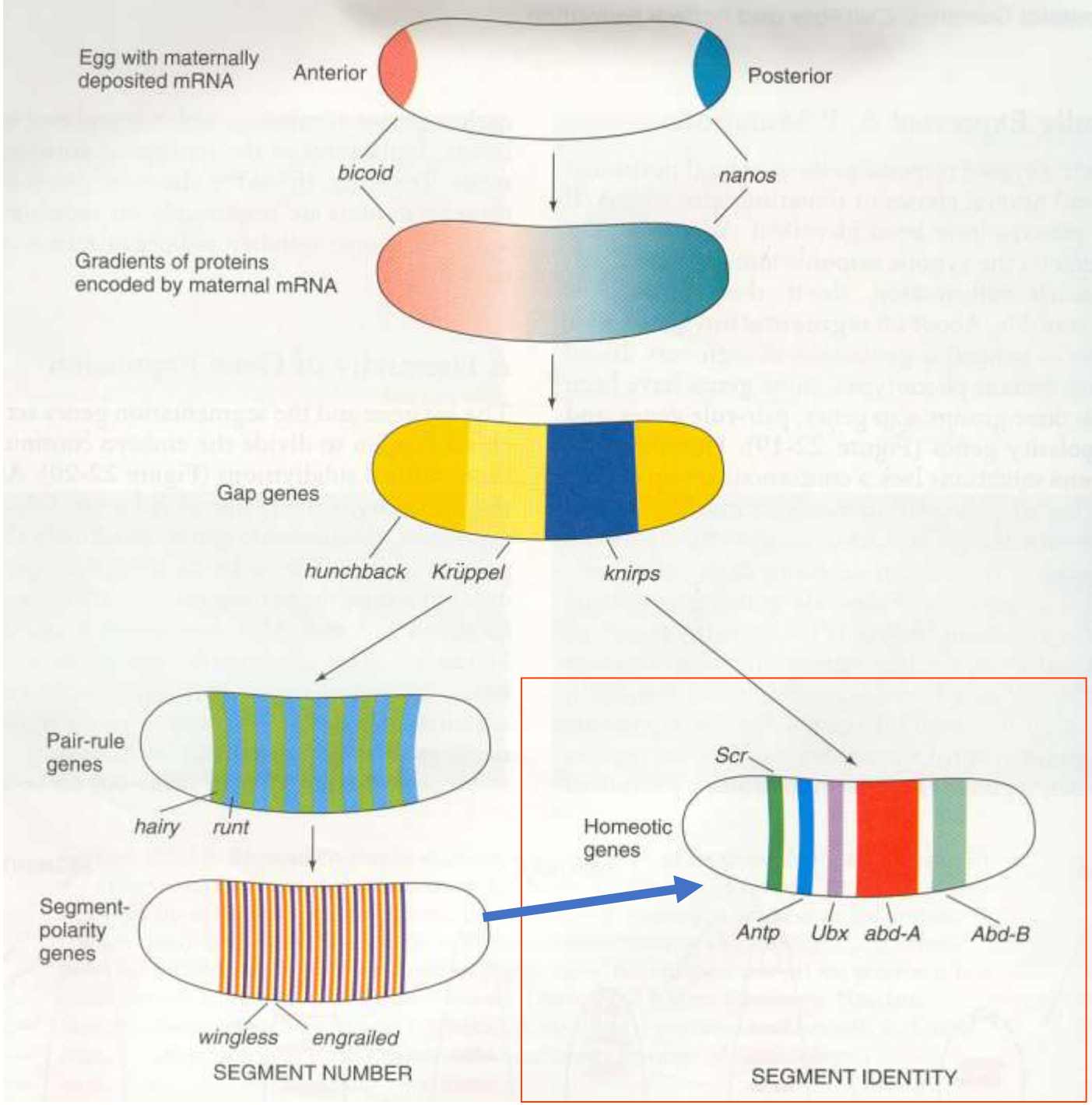
(b) Homeotic protein bound to DNA

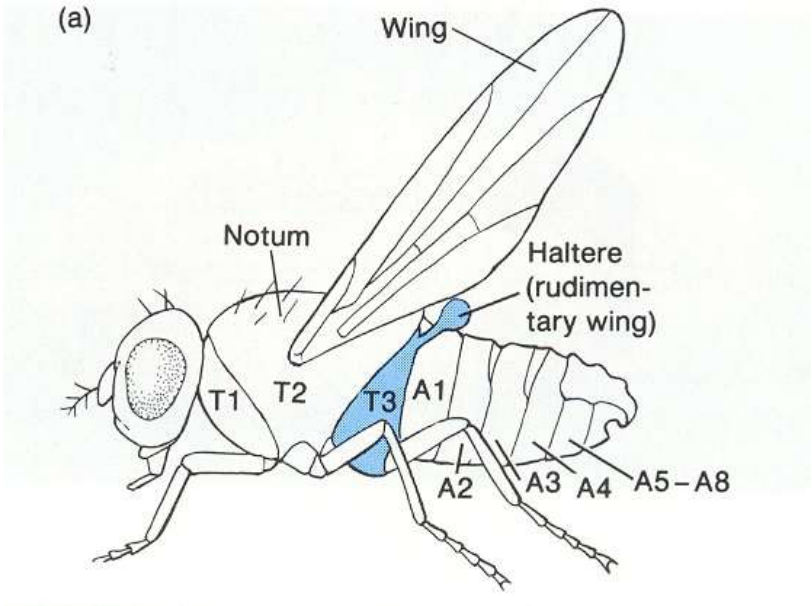
HOX fehérjék - transzkripciós faktorok

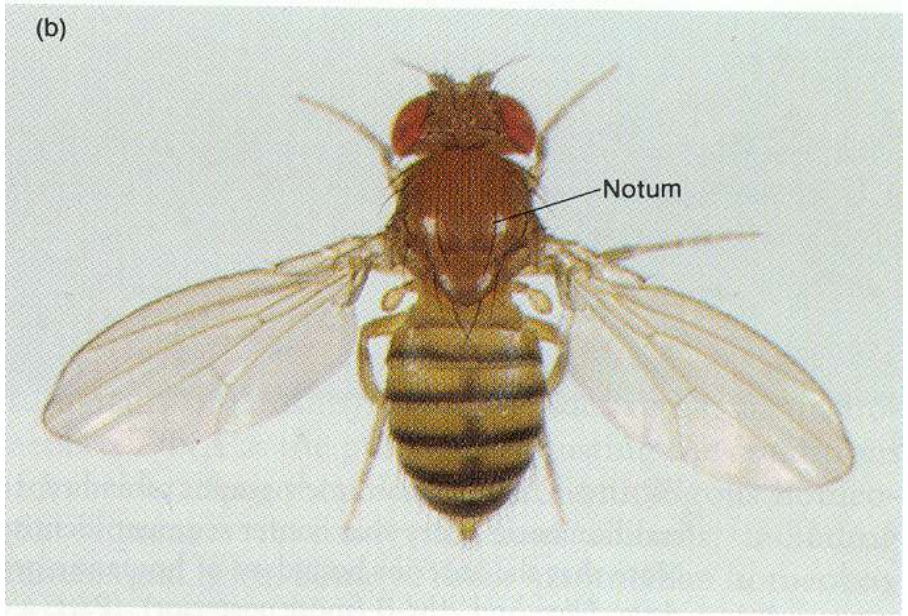
Evolution of Hox genes: through tandem gene duplications

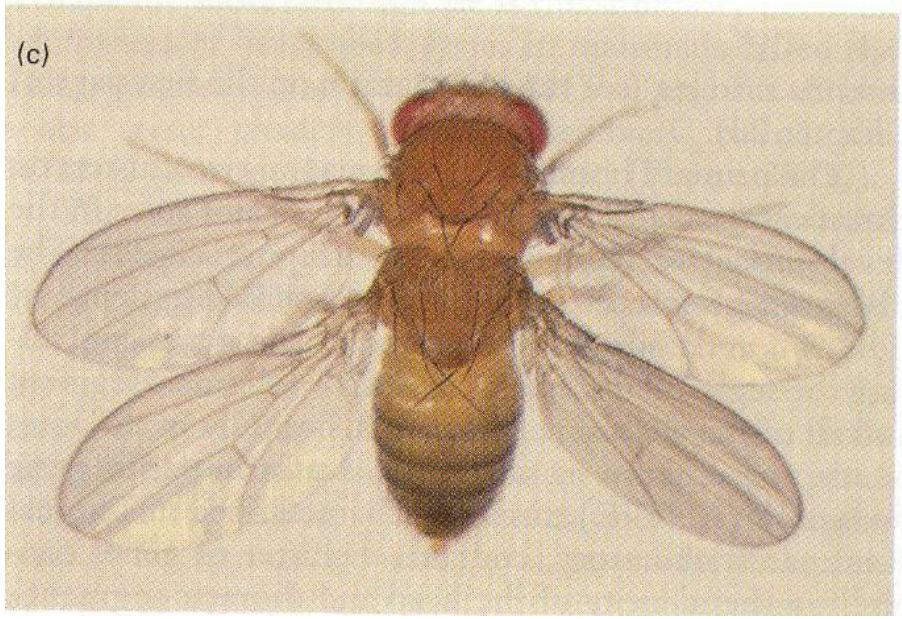


Drosophila early development (cascade of genes)









Drosophila Hox mutants

bithorax mutant

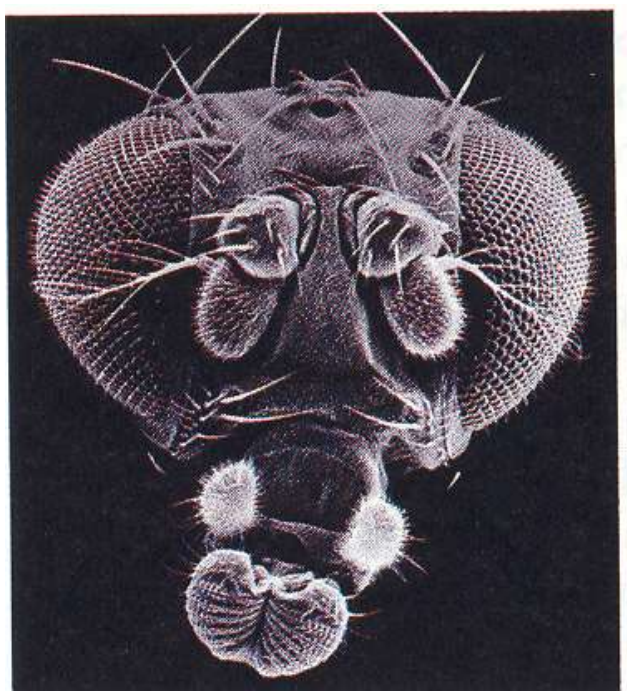
Edward Lewis, Nobel prize, 1995

(homeotic transformation - rearrangement of the body)

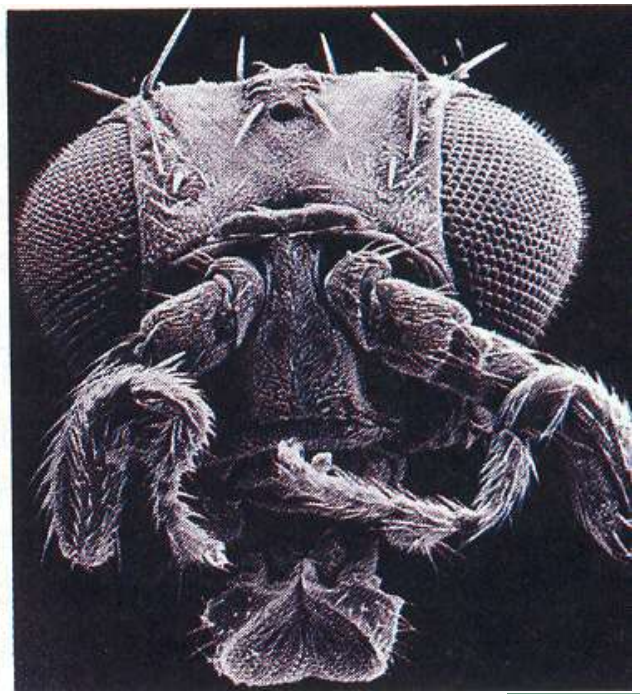
for their discoveries concerning the genetic control of early embryonic development".

Drosophila Hox mutants.

Drastic rearrangement of the body (homeotic transformation)

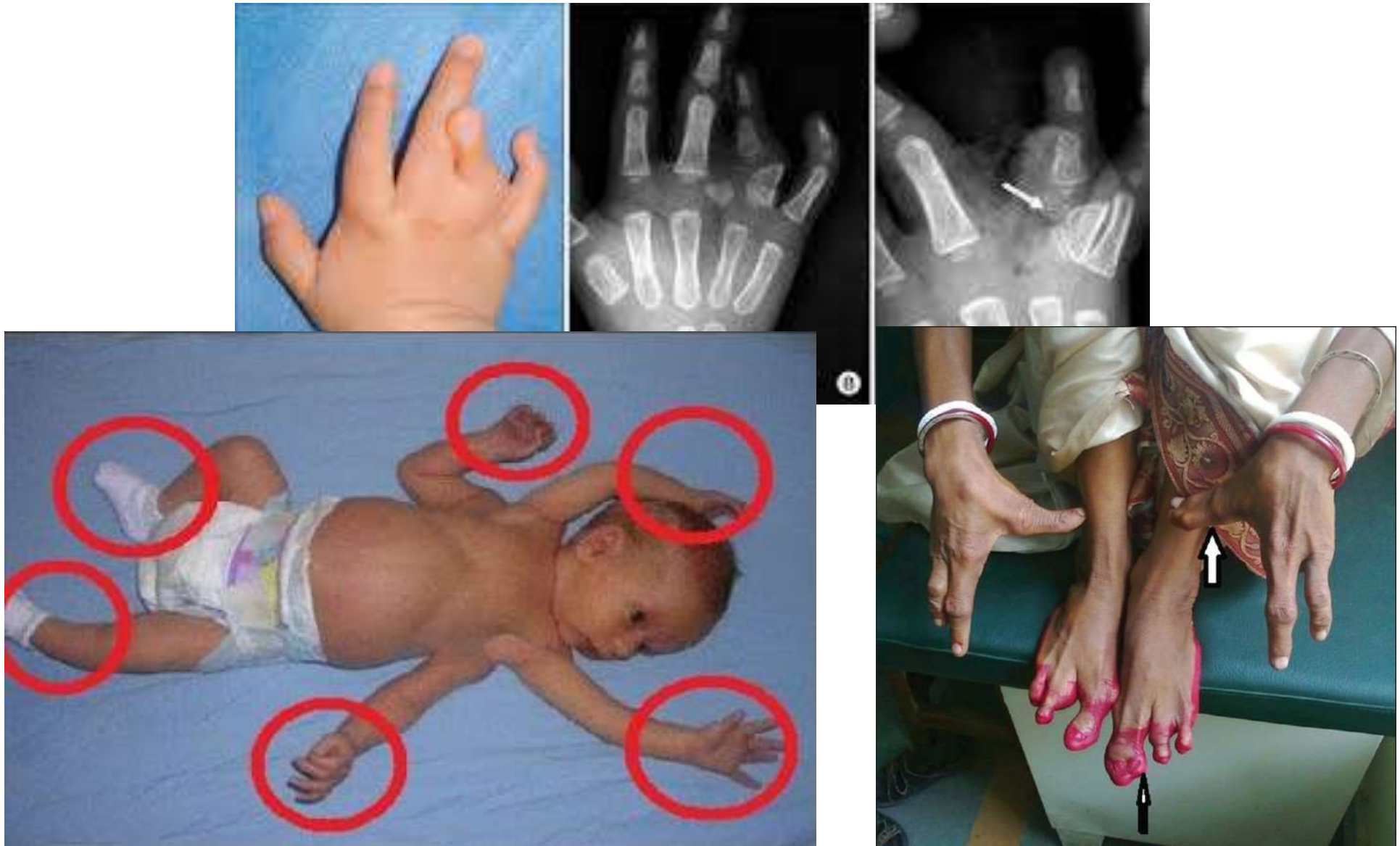


Wild type

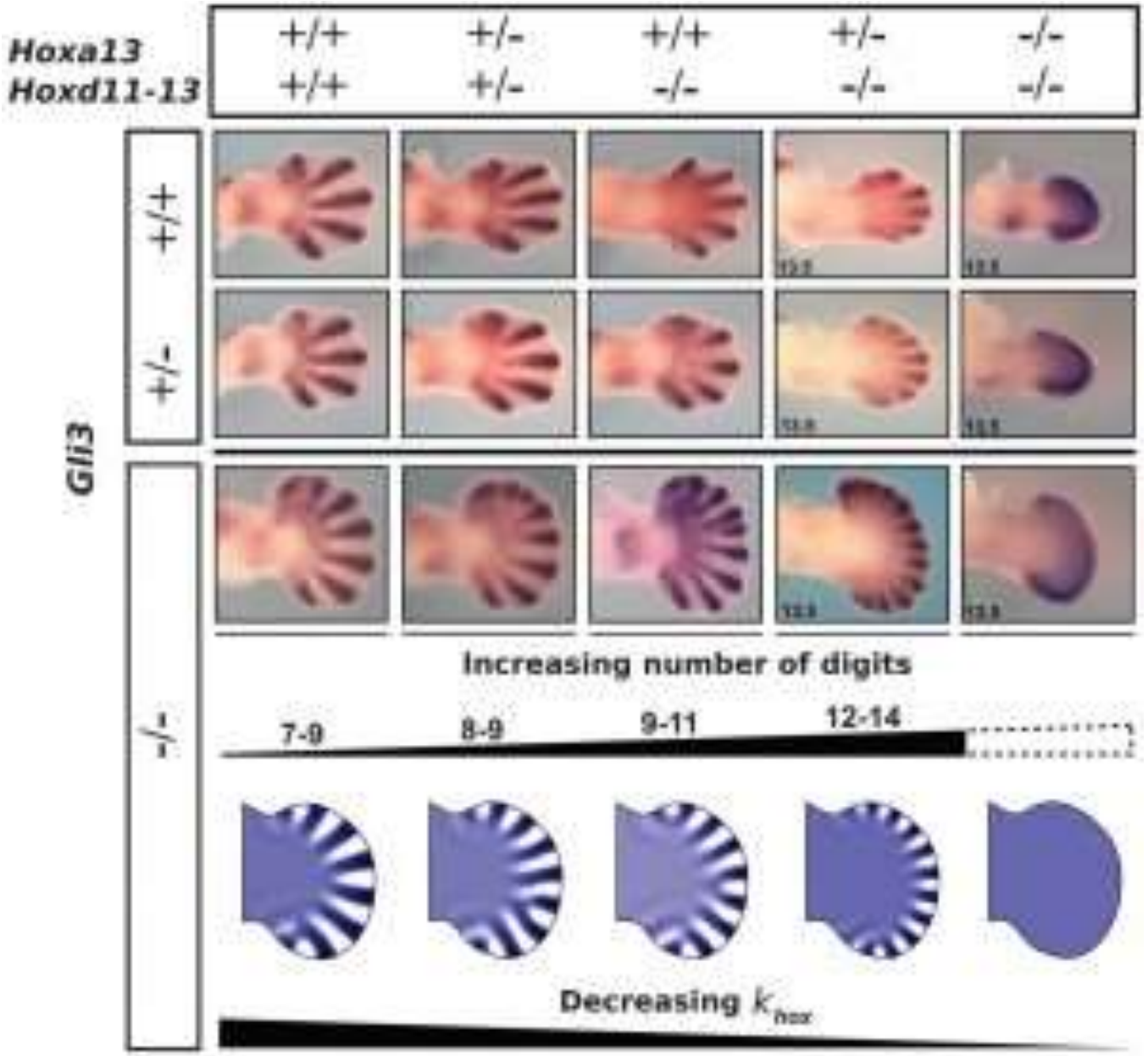


Antp mutant
(dominant)

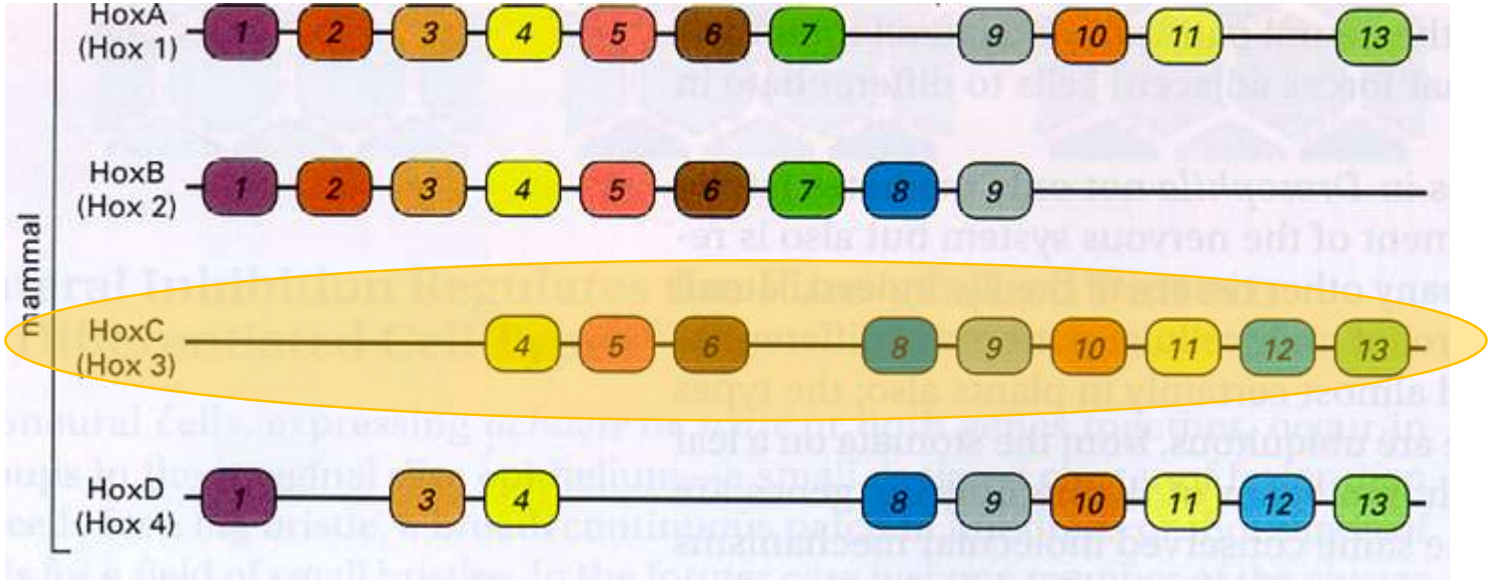
Human *Hox* mutations

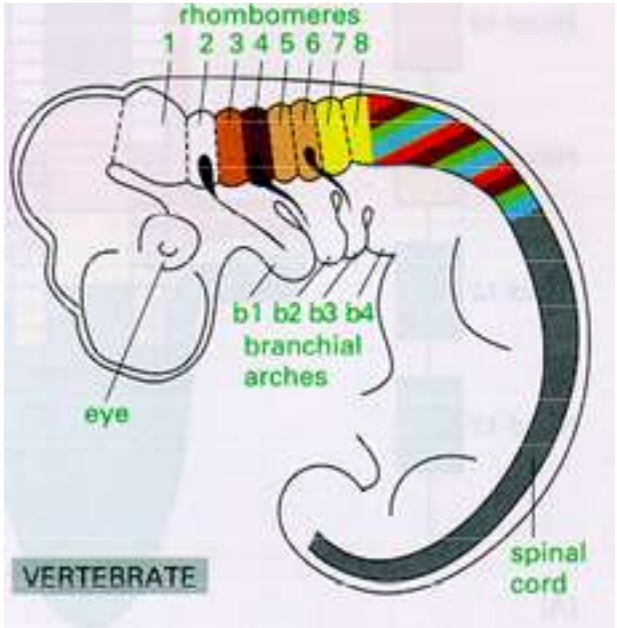


Hox genes in limb development



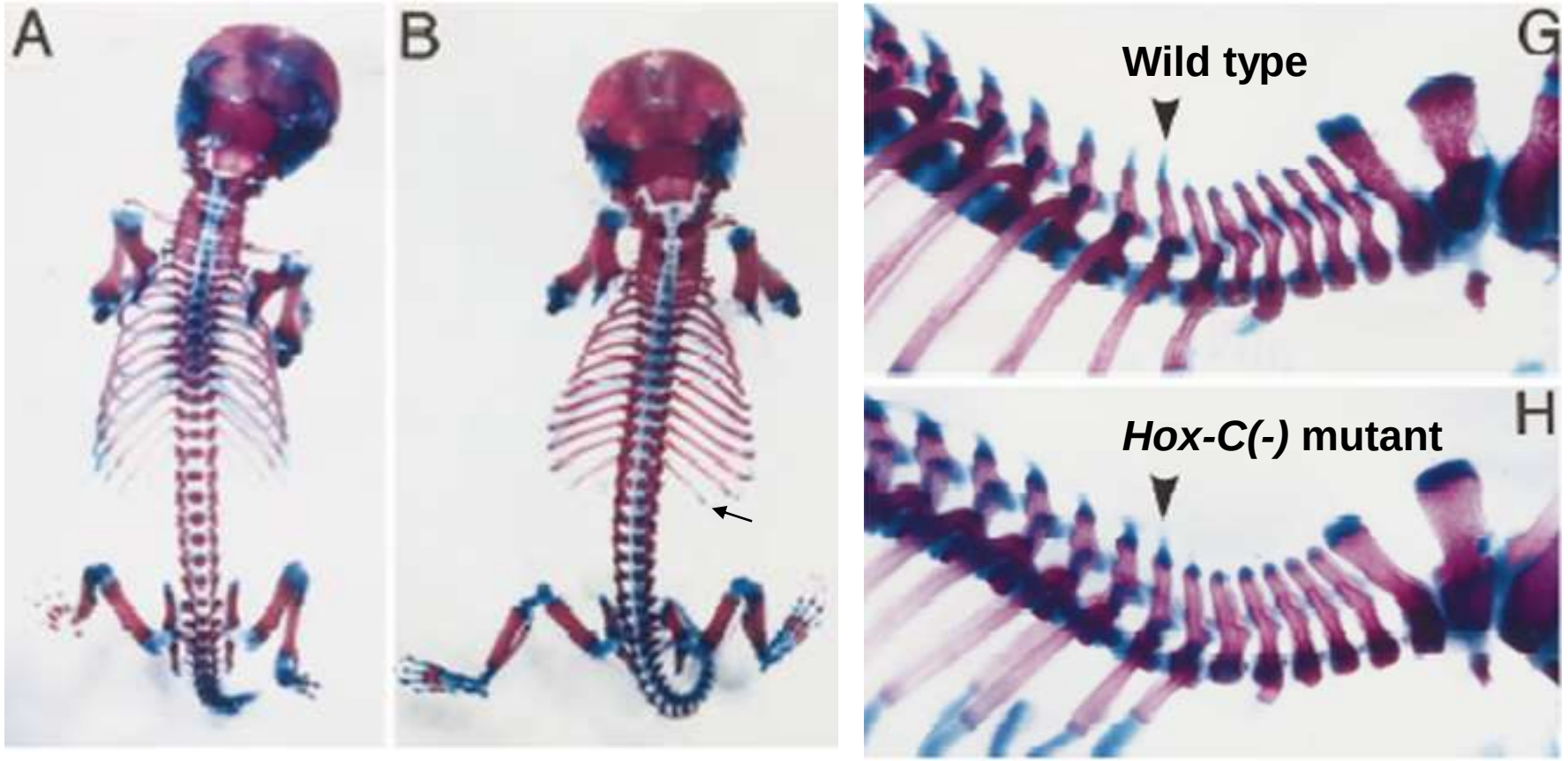
Mammalian *Hox clusters*





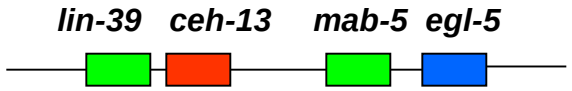
Functional redundancy between Hox clusters

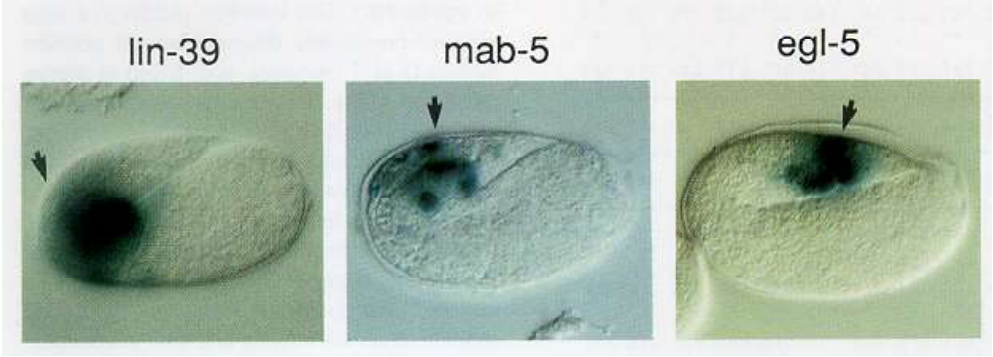
Deletion of the entire Hox-C cluster causes minor changes in mouse development.



Collinearity of Hox genes

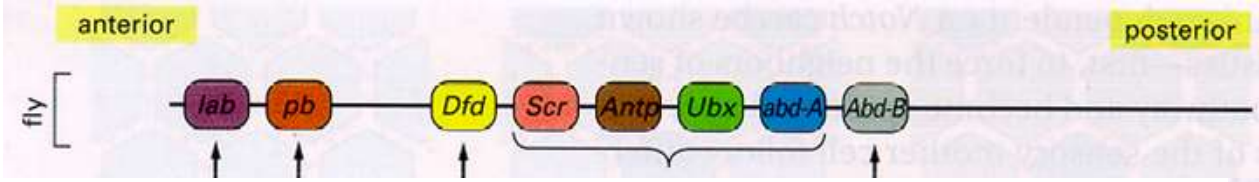
C. elegans

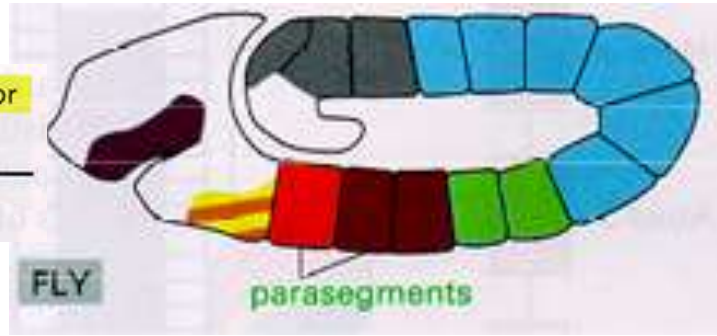




Their spatial-temporal expression is a function of their genomic position: the upstream component in the cluster is anterior and early in time.

D. melanogater





HOX proteins become specific with co-factors (cannot bind to specific sequences alone)

HOX protein is secondary - promoter (regulation) gives its specificity.

TF hierarchy during hematopoiesis

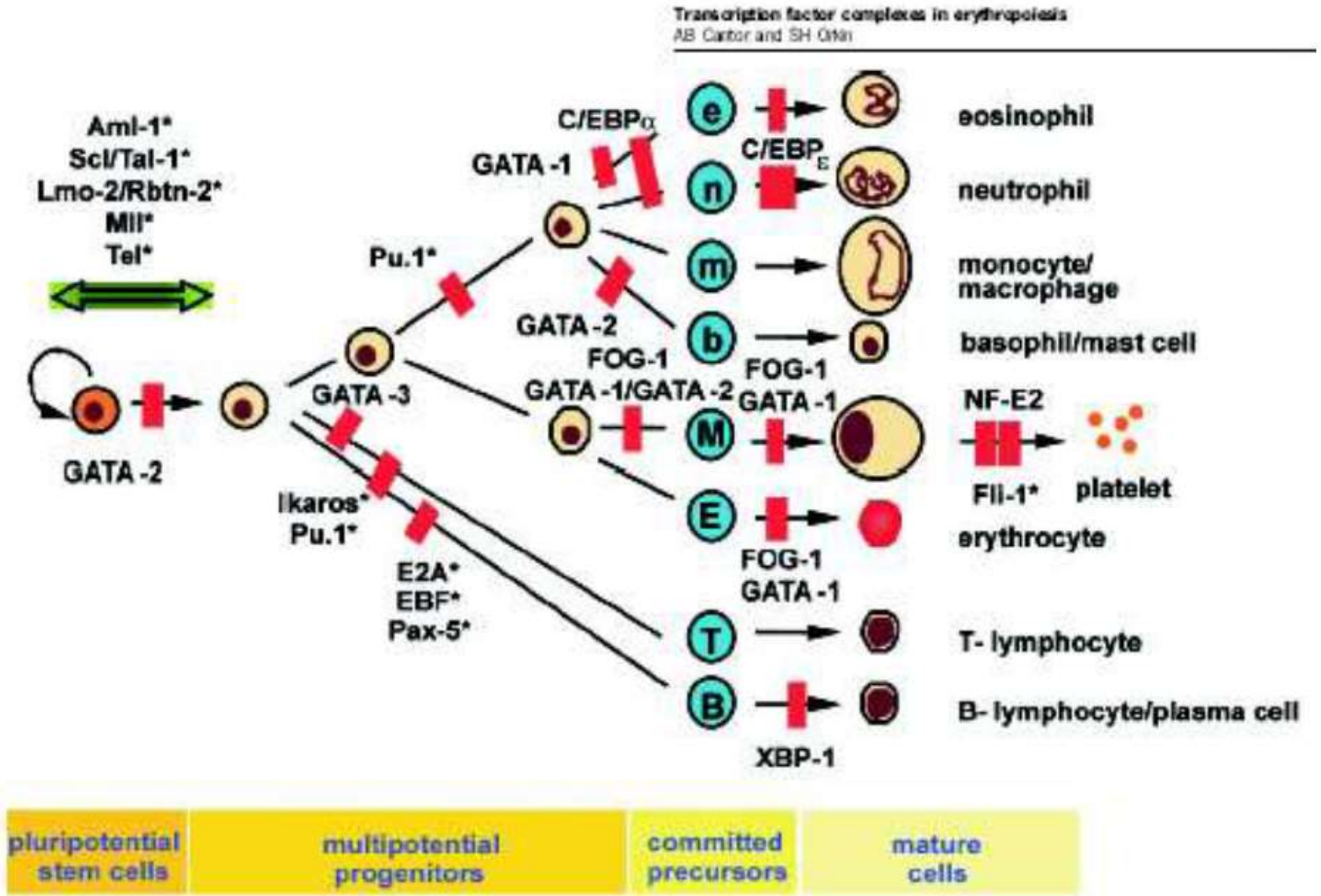
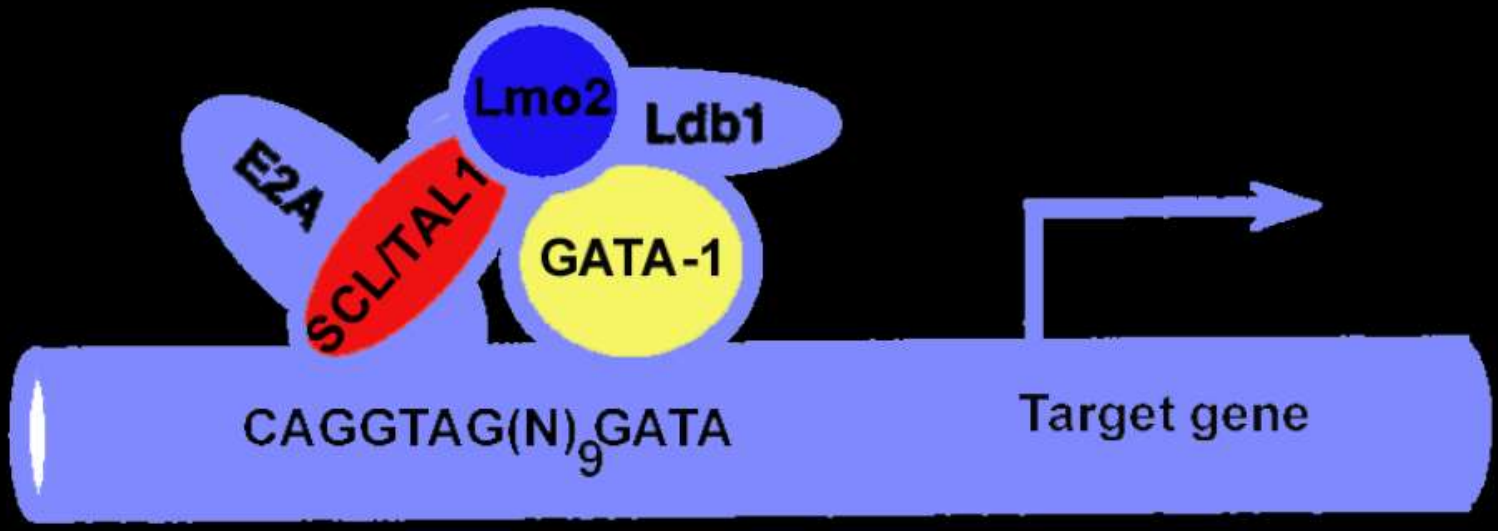


Figure 1 Transcription factor requirements in hematopoiesis. Schematic representation of hematopoietic lineage pathways from pluripotential stem cells to mature blood elements. Red bars represent the location of maturation arrest observed in the absence of the corresponding transcription factor. Transcription factors associated with chromosomal translocations or viral insertions in human and murine leukemias are denoted by an asterisk. e, eosinophil; n, neutrophil; m, monocyte/macrophage; b, basophil/mast cell; M, megakaryocyte; E, erythrocyte; T, T-lymphocyte; B, B-lymphocyte

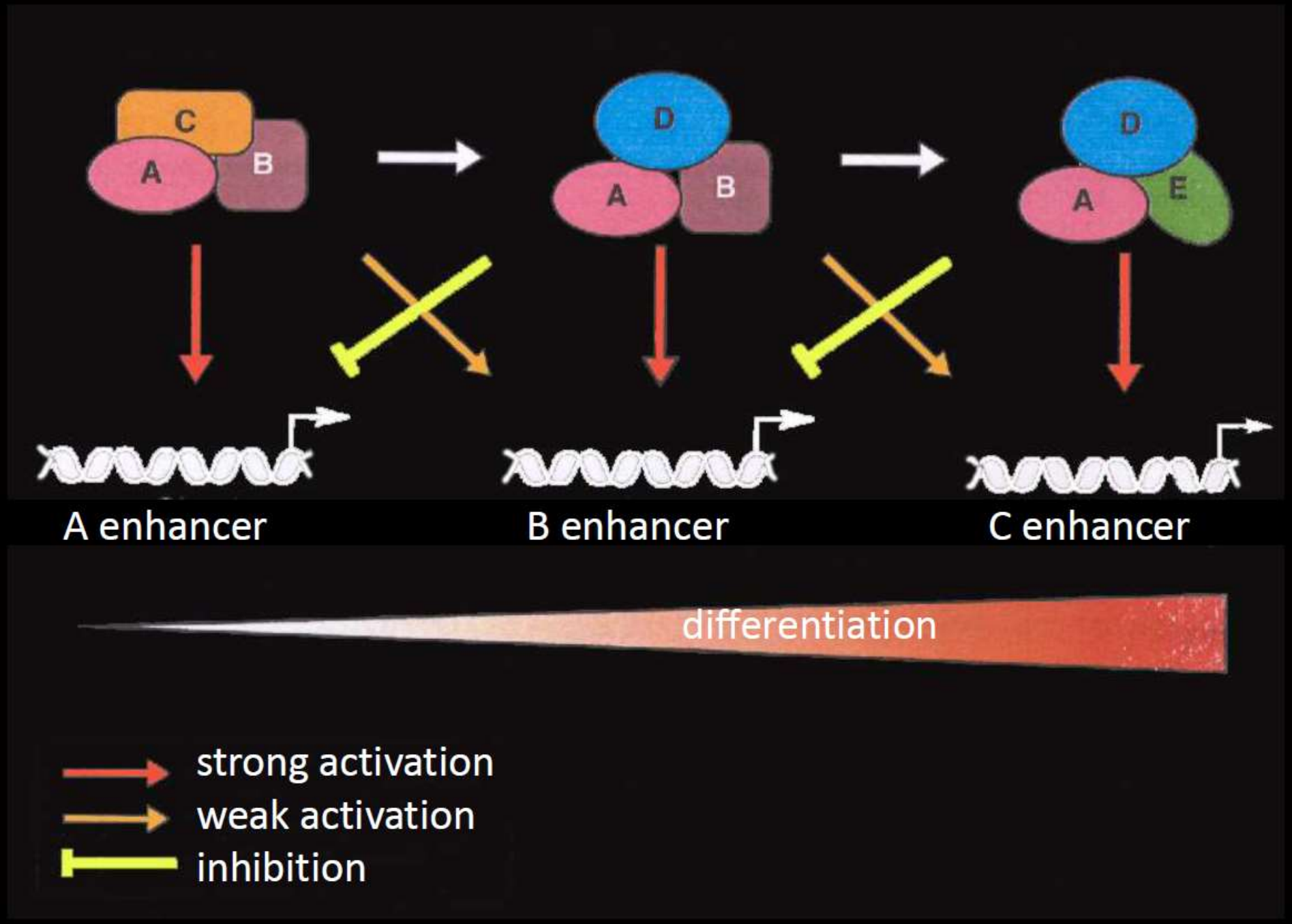
Combinatorial action of transcription factors

Fig. 8. Model of the Lmo2-containing oligomeric DNA-binding complex. The oligomeric complex binds to the E-box–GATA motif with a restricted spacing of 9 bp (at least as determined by CASTing with the R76 oligonucleotide). The stoichiometry of the complex is unknown, but DNA-binding modules within the oligomeric complex are provided by E47–TAL1 heterodimer (E-box binding) and GATA-1 (GATA binding). The Lmo2 LIM-only protein, together with Ldb1, links the two DNA-binding moieties. Target genes with E-box–GATA motif(s) provide recognition sites for the oligomeric complex. Transcriptional transactivation of these genes is a possible consequence of binding to target genes, but repressive functions may also occur, perhaps depending on the stage of haematopoiesis at which binding occurs.

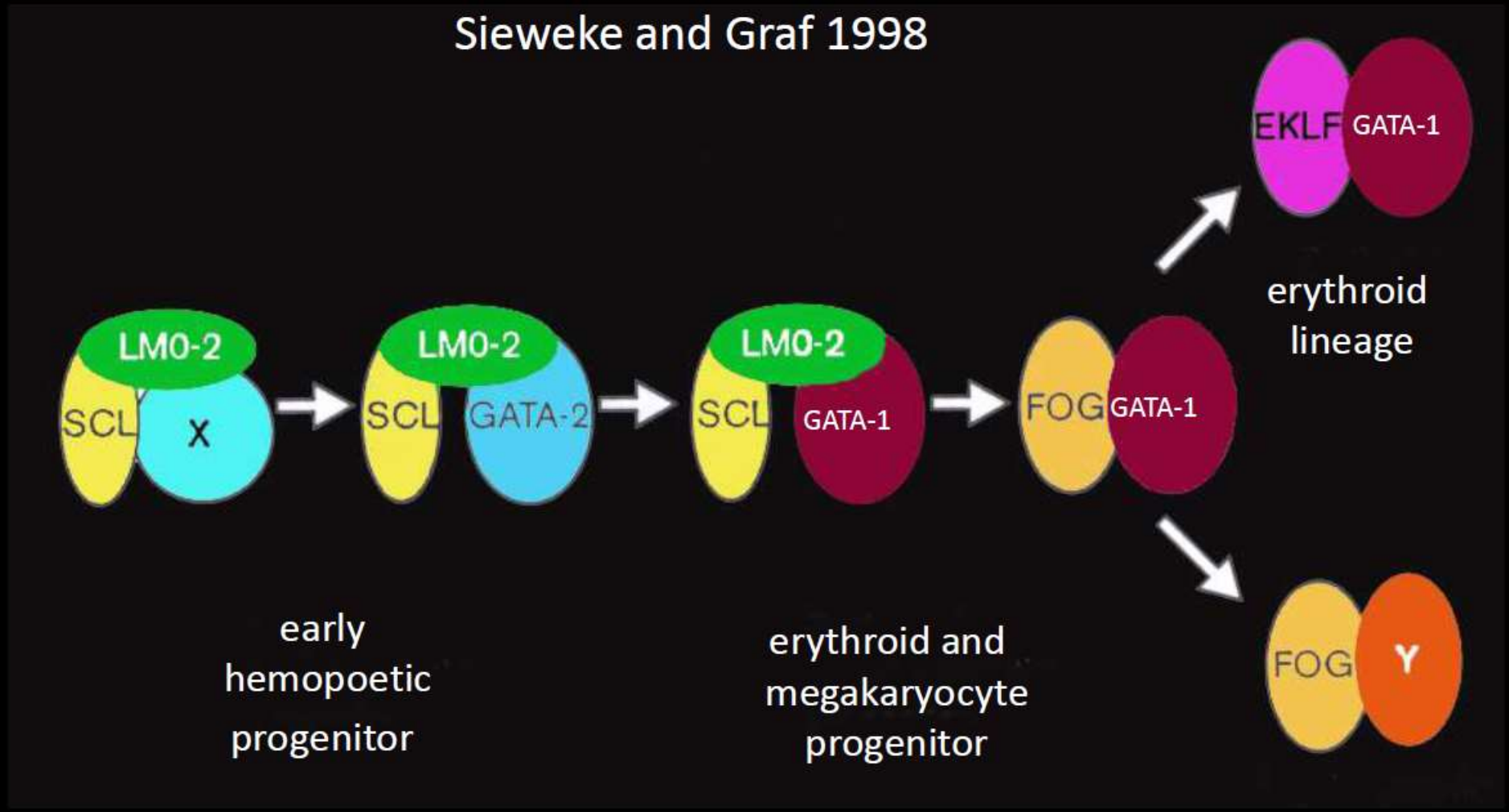


Wadman et al. 1997 The EMBO Journal 16: 3145–3157

In the commitment of cell lineages, lineage-specific transcription factors (TF), working with general TFs play important roles. In addition, lineage-specific gene expression appears to be regulated not by single master regulators but by the combinations of transcription factors (160). Expression of a given transcription factor may have different consequences in different cell types, in part because of the different transcriptional environment. The combinatorial action of transcription factors is more important in the control of gene expression, which occurs by many physically interacting factors, forming large, multiprotein complexes. During differentiation, lineage specific complexes are selected, and define the direction of commitment. Sieweke and Graf suggested in their model that these complexes obtain new functions during haematopoietic differentiation through successive changes in composition, such as the topic of discussion changes and take other directions as new people join and others leave a cocktail party. The changes in the composition drive to sequential gene expression activations and inhibitions responsible for specific determination and differentiation (161).

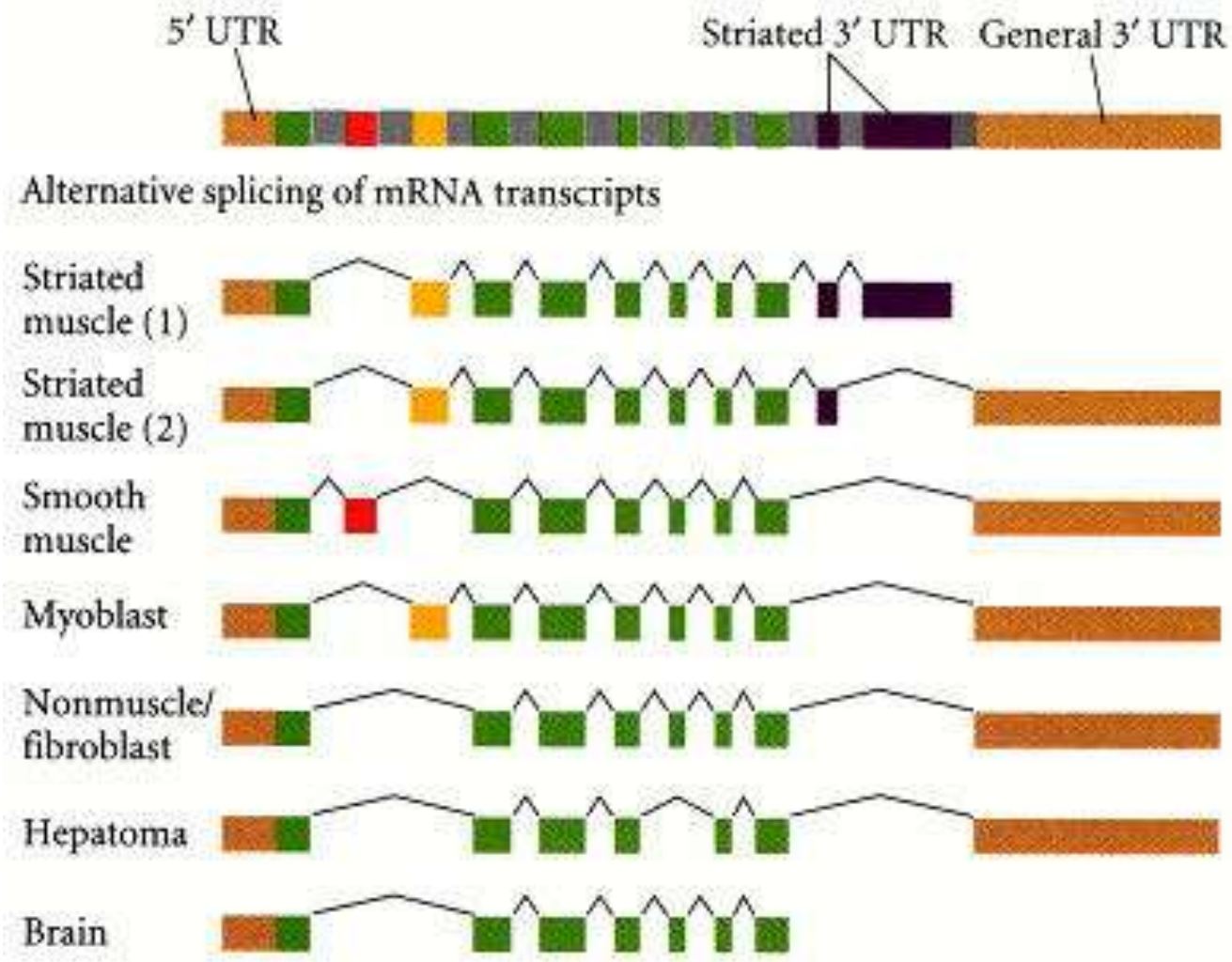

C
A
B
D
A
B
D
A
E
A enhancer
B enhancer
C enhancer
differentiation
strong activation
weak activation
inhibition

The „coctail party" model



Posttranscriptional regulation

Alternative RNA splicing: a family of rat α-tropomyosin proteins

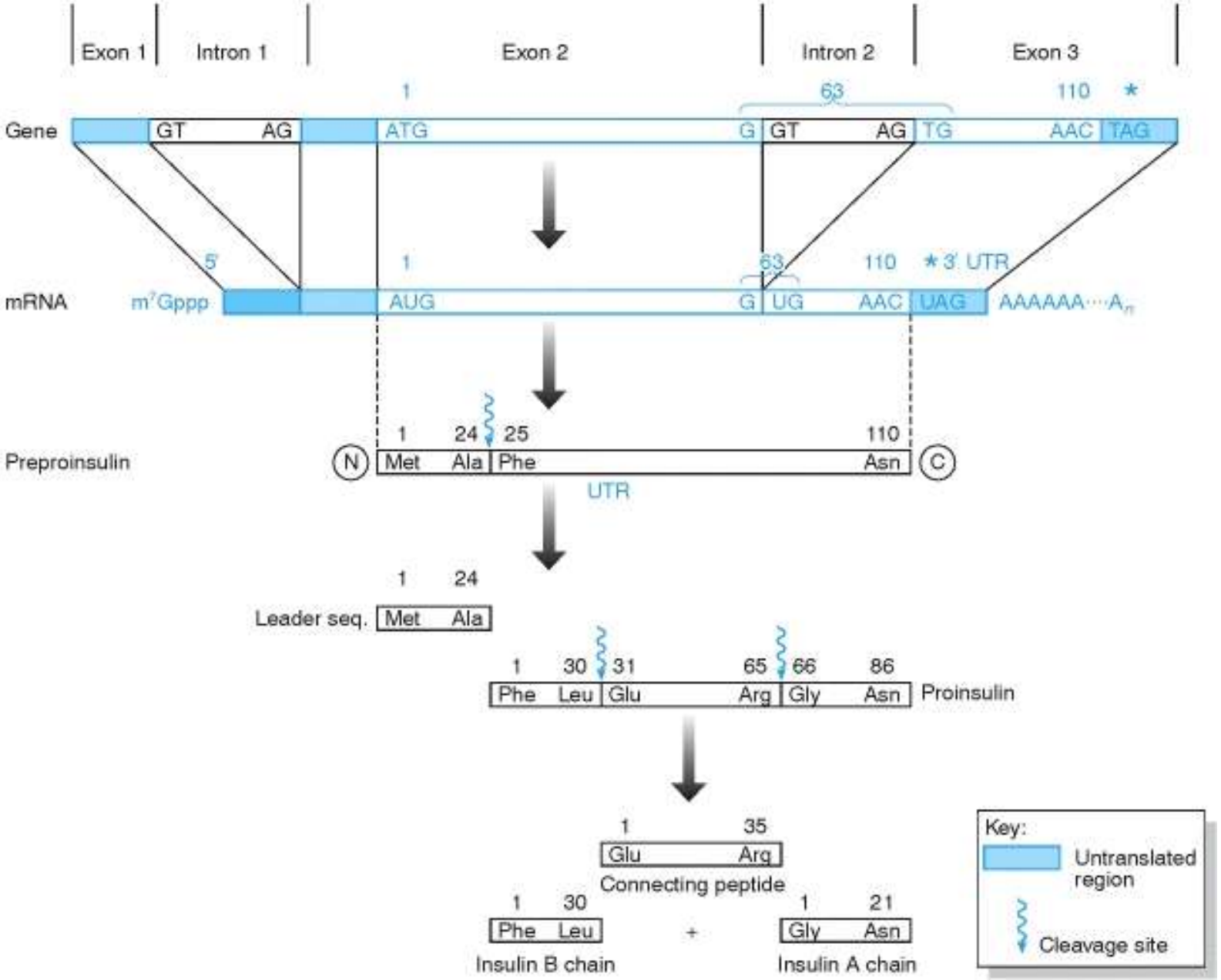


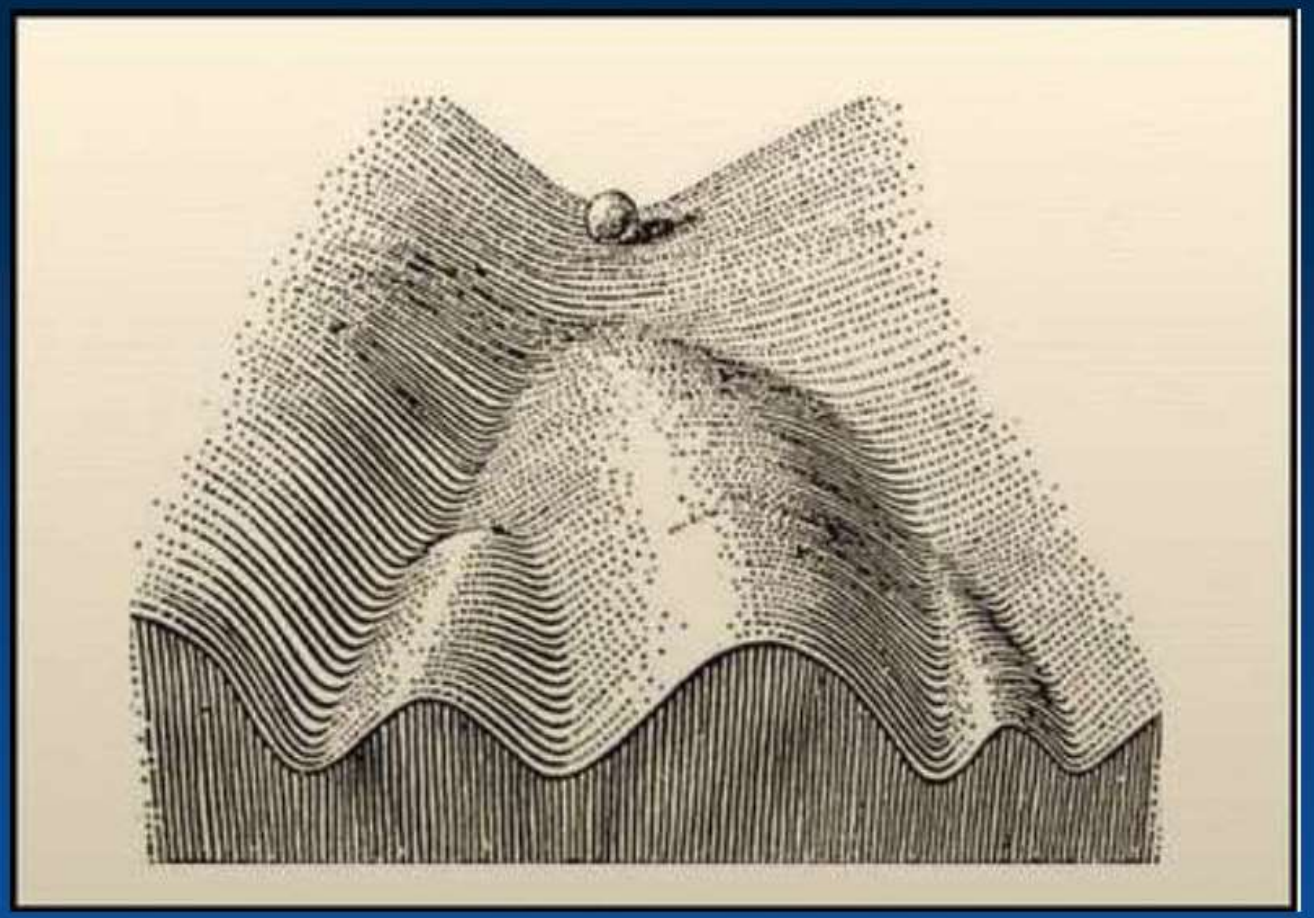
Post-translational level of gene regulation

Major types of post-translational modifications of polypeptides

Type of modification (group added)	Target amino acids	Comments
Phosphorylation (PO_4^-)	Tyrosine, serine, threonine	Achieved by specific kinases. May be reversed by phosphatases
Methylation (CH_3)	Lysine	Achieved by methylases and undone by demethylases
Hydroxylation (OH)	Proline, lysine, aspartic acid	Hydroxyproline and hydroxylysine are particularly common in collagens
Acetylation (CH_3CO)	Lysine	Achieved by an acetylase and undone by deacetylase
Carboxylation (COOH)	Glutamate	Achieved by γ-carboxylase
N-glycosylation (complex carbohydrate)	Asparagine, usually in the sequence: **Asn**-X-Ser/Thr	Takes place initially in the endoplasmic reticulum; X is any amino acid other than proline
O-glycosylation (complex carbohydrate)	Serine, threonine, hydroxylysine	Takes place in the Golgi apparatus; less common than *N*-glycosylation
GPI (glycolipid)	Aspartate at C terminus	Serves to anchor protein to *outer* layer of plasma membrane
Myristoylation (C_{14} fatty acyl group)	Glycine at N terminus (see text)	Serves as membrane anchor
Palmitoylation (C_{16} fatty acyl group)	Cysteine to form S-palmitoyl link.	Serves as membrane anchor
Farnesylation (C_{15} prenyl group)	Cysteine at C terminus (see text)	Serves as membrane anchor
Geranylgeranylation (C_{20} prenyl group)	Cysteine at C terminus (see text)	Serves as membrane anchor

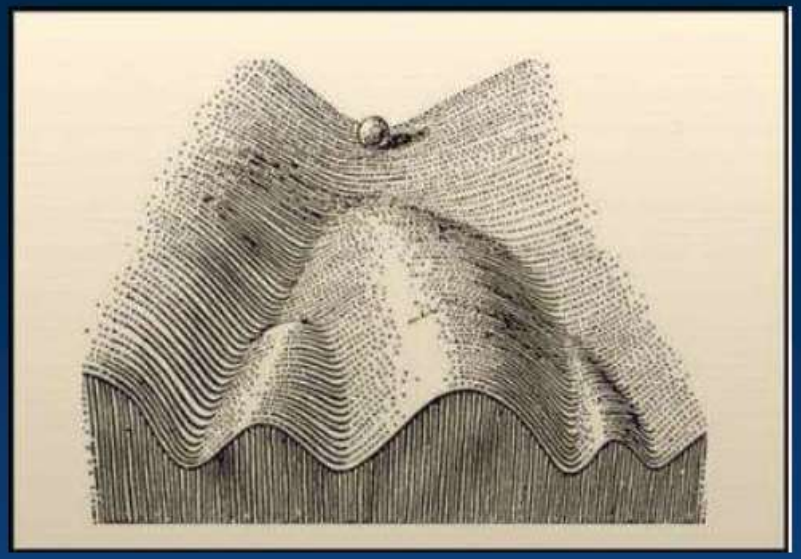
During insulin synthesis, polypeptide precursors undergo multiple post-translational cleavage:





Conrad Hal Waddington (November 8, 1905 – September 26, 1975) postulated that it was not just the genes that shaped development but also the environment that shape the genes.

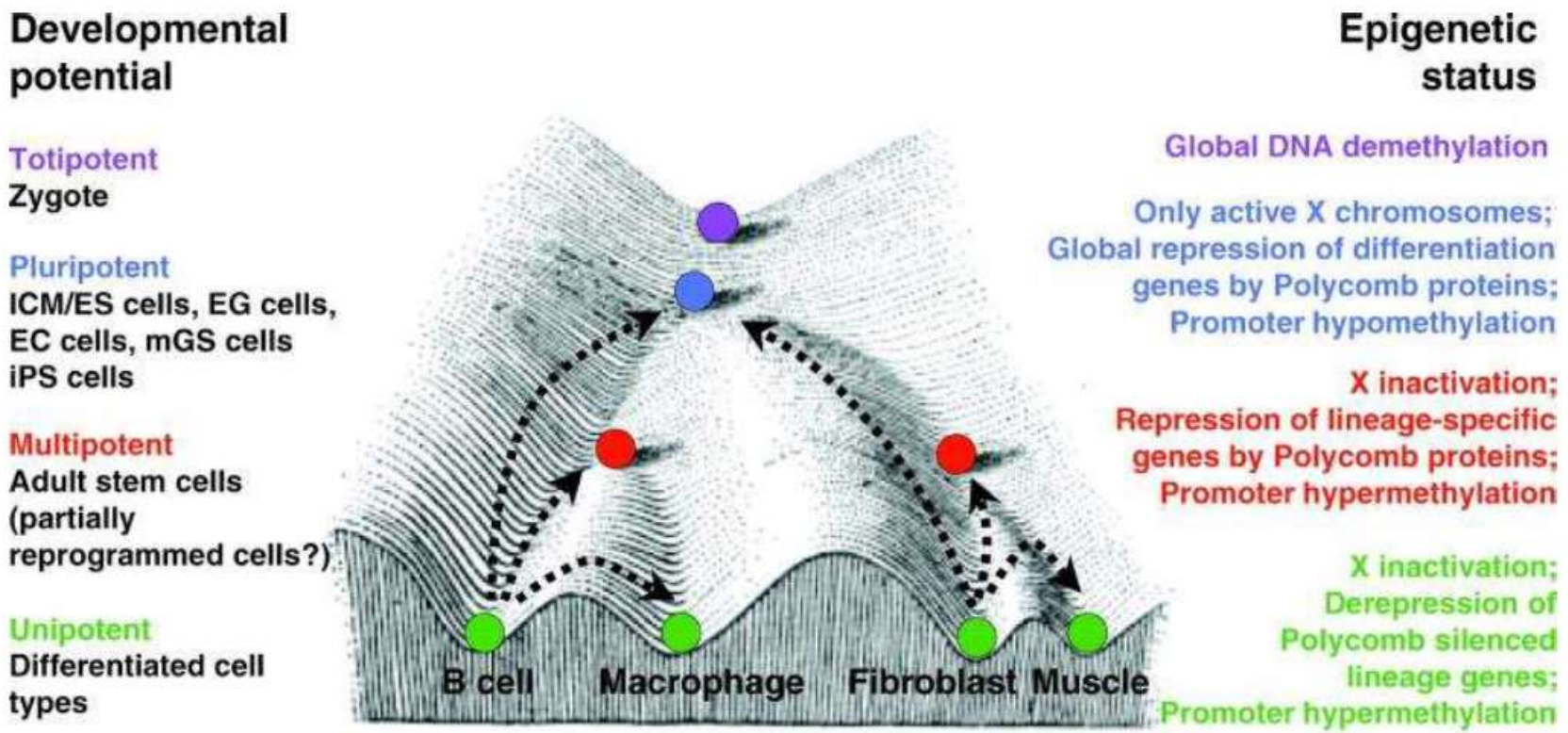
EPIGENETICS: external manifestation of genetic activity



Epigenetic landscape

Waddington's epigenetic landscape is a metaphor for how gene regulation modulates development.[8] One is asked to imagine a number of marbles rolling down a hill towards a wall. The marbles will compete for the grooves on the slope, and come to rest at the lowest points. These points represent the eventual cell fates, that is, tissue types. Waddington coined the term Chreode to represent this cellular developmental process. This idea was actually based on experiment: Waddington found that one effect of mutation (which could modulate the epigenetic landscape) was to affect how cells differentiated. He also showed how mutation could affect the landscape and used this metaphor in his discussions on evolution—he was the first person to emphasise that evolution mainly occurred through mutations that affected developmental anatomy.

The developmental potential and epigenetic states of cells at different stages of development.



The developmental potential and epigenetic states of cells at different stages of development. A modification of C. H. Waddington's epigenetic landscape model, showing cell populations with **different developmental potentials** (left) **and their respective epigenetic states** (right). Developmental restrictions can be illustrated as marbles rolling down a landscape into one of several valleys (cell fates). Colored marbles correspond to different differentiation states (purple, totipotent; blue, pluripotent; red, multipotent; green, unipotent). Examples of reprogramming processes are shown by dashed arrows. Adapted, with permission, from Waddington (Waddington, 1957).

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Hochedlinger K , Plath K Development 2009;136:509-52
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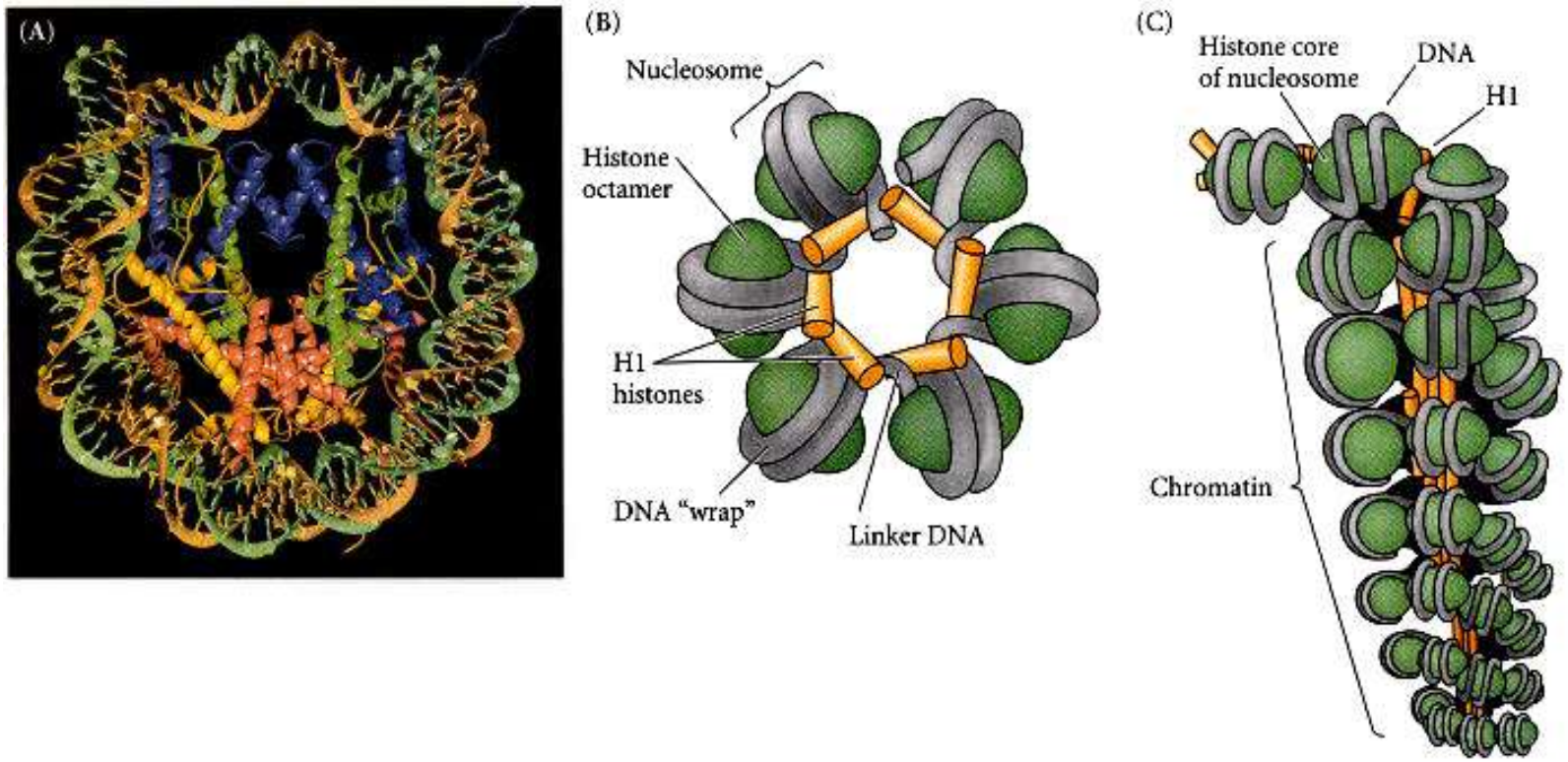
Nucleosome and chromatin structure

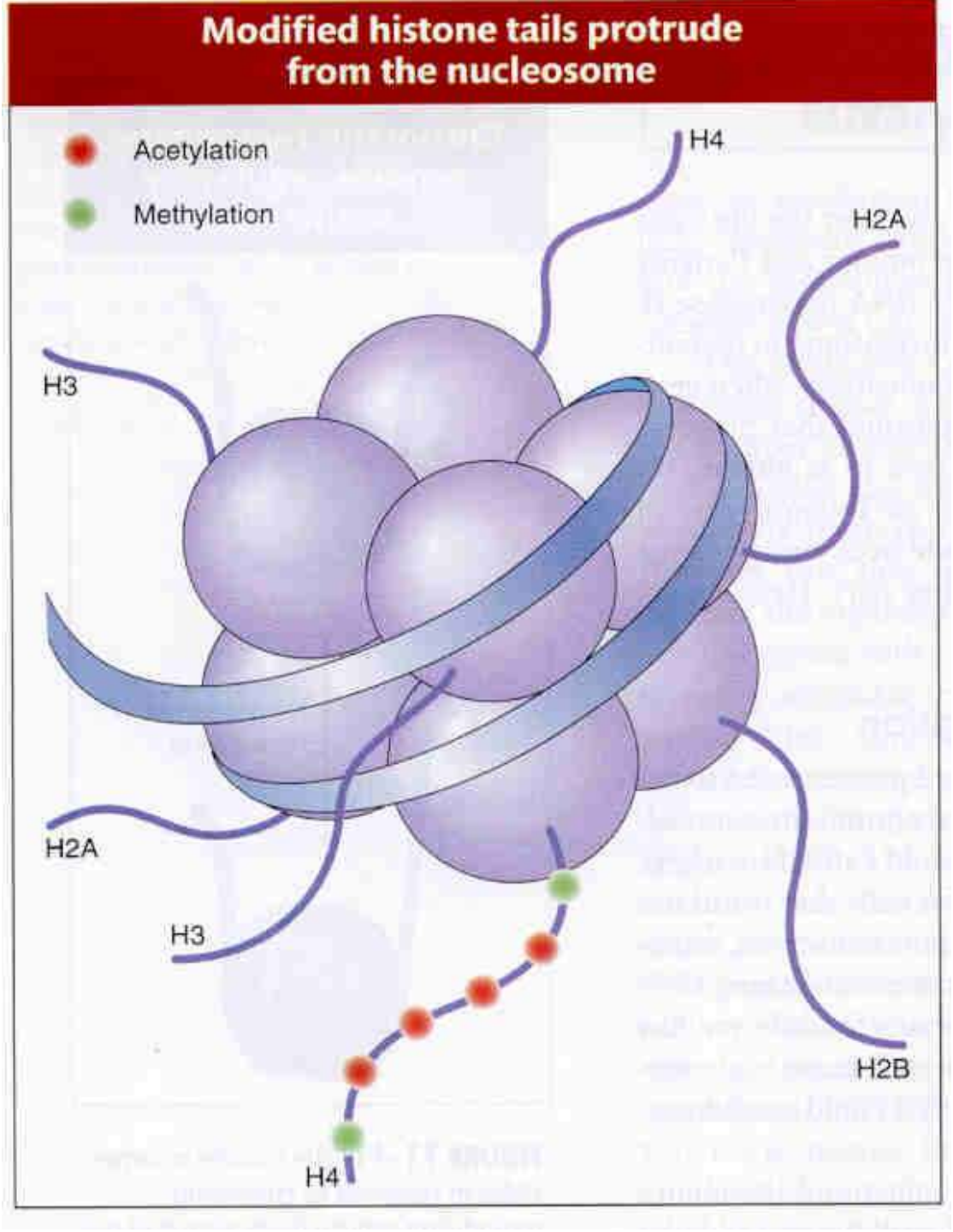
prokaryotic genes at baseline "On" while the eukaryote genes are "off."



A nucleosome is a basic unit of chromatin, where a segment of DNA is wound around a histone octamer (consists of H2A, H2B, H3 and H4 histones). Nucleosomes are ordered into higher structures (fibers) by H1 histones.

Histone tails can be posttranslationally modified at given poistions (often lysines): acetylation, methylation, phosphorylation (on serine), ubiquitination.

Histone code: epigenetic inheritance



Chromatin remodeling

- The organization of the chromatin poses a barrier to transcription, because it prevents direct interaction of the transcription machinery and the promoters.
- Chromatin remodeling enzymes alter the folding, fluidity and basic structure of chromatin, such as histone acetyltransferases (HATs, Gcn5p, pCAF, p300/CBP), ATP-dependent remodeling enzymes (SWI/SNF).
- **Acetylation of histones: destabilization of nucleosomes!**
- **Destabilization of nucleosomes allows gene expression:** transcription factors recruit histone acetyltransferases, resulting in binding of transcription factors and RNA polymerase II to the promoter.
- **Deacetylation stabilizes the chromatin:** histone deacetylases (HDAC), methyltransferases (methyl-DNA binding protein: MBD) function in other complexes, such as the NuRD (nucleosome remodeling) complex.

The histone octamer slides in response to chromatin-remodeling activity, in this case exposing the DNA marked in red.

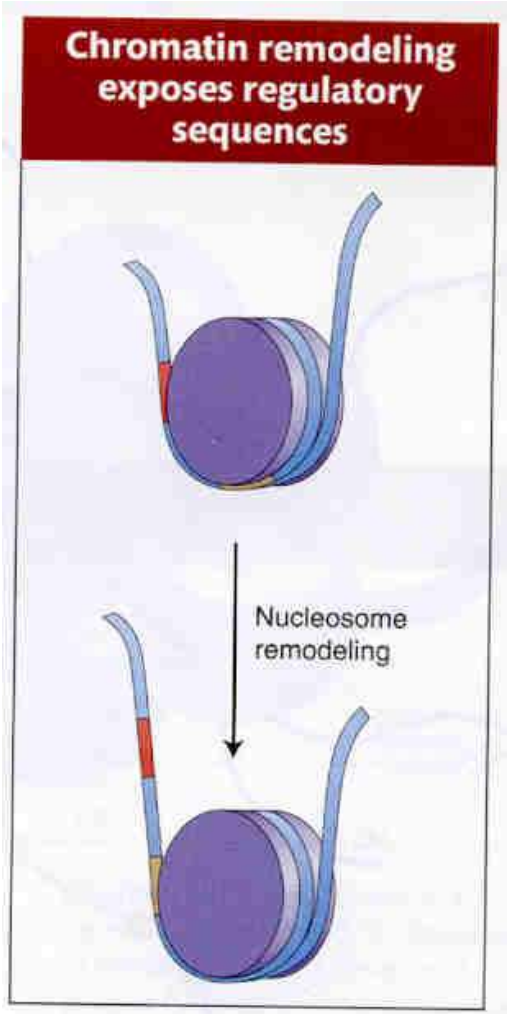
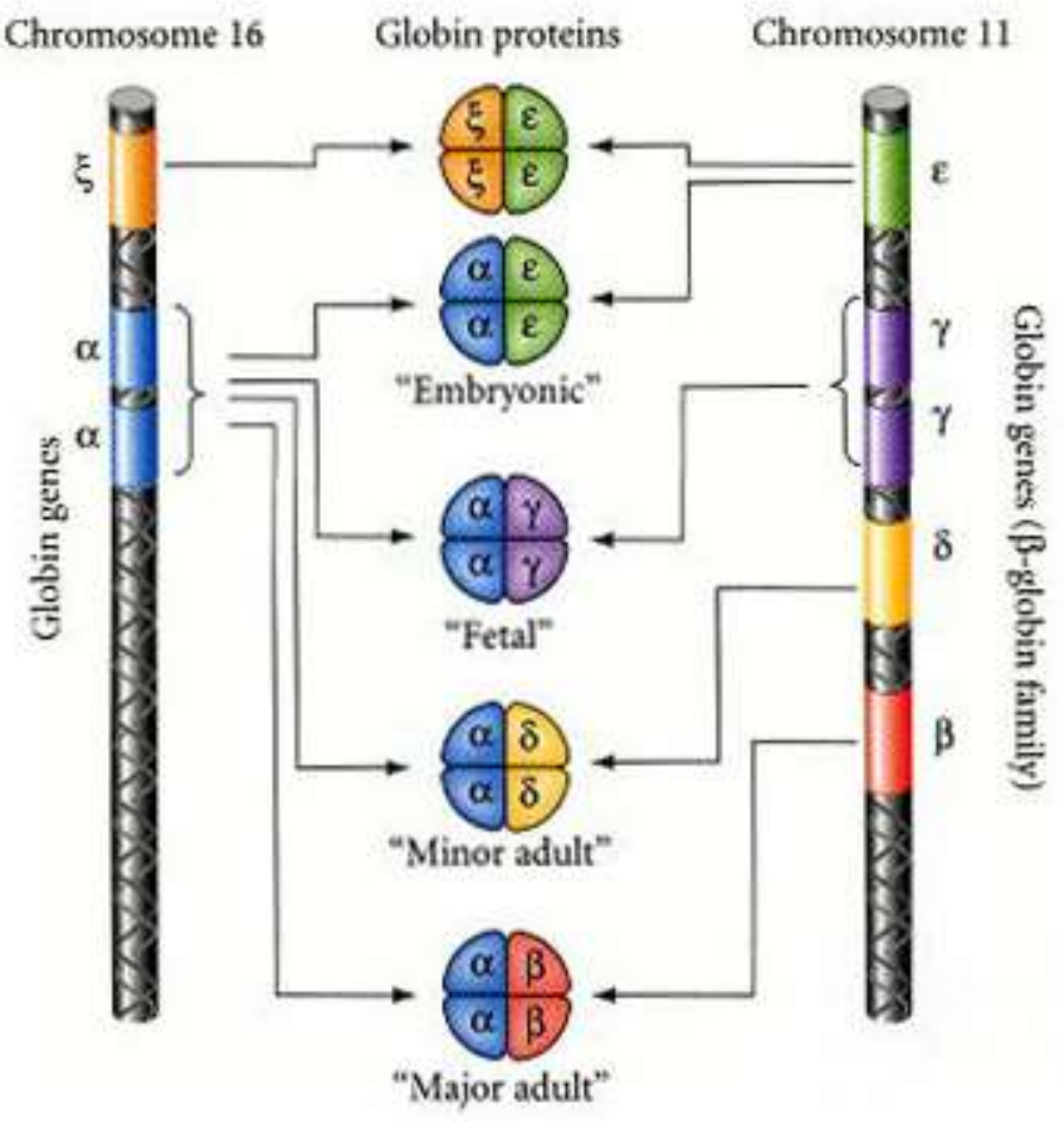
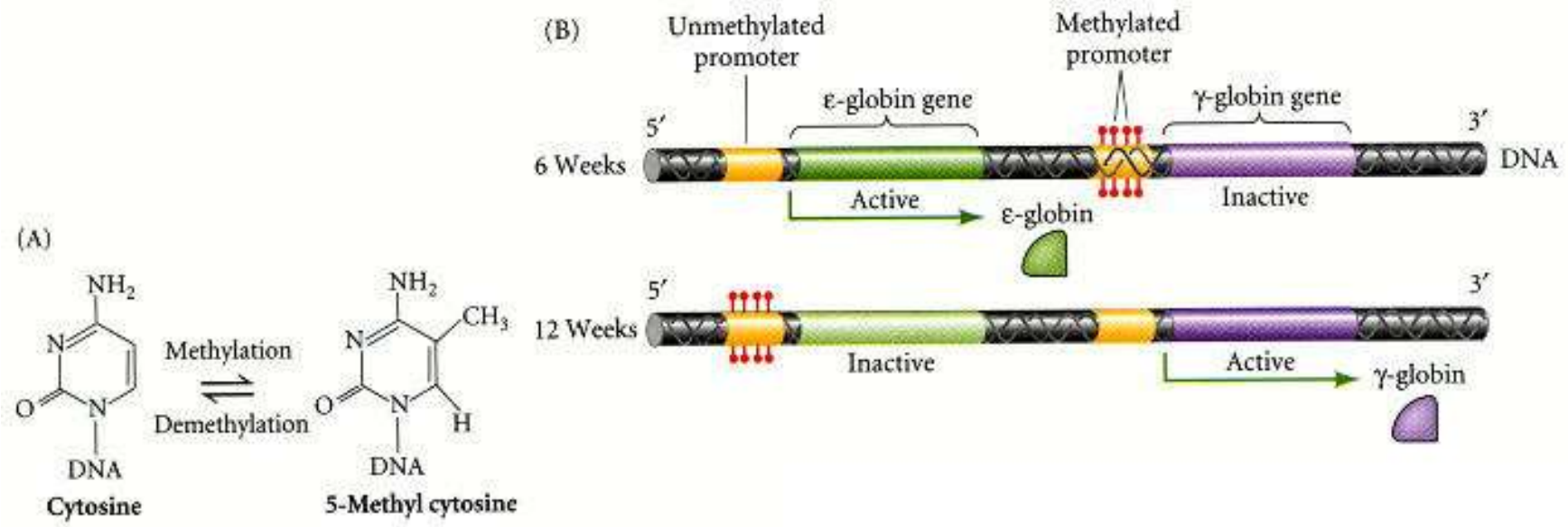


FIGURE 11-11 The histone octamer slides in response to chromatin-remodeling activity (such as that of the SWI-SNF complex), in this case exposing the DNA marked in red. (See Figure 11-15 for details on how SWI-SNF is recruited to a particular DNA region). [After J. Watson et al., *Molecular Biology of the Gene*, Fifth Edition, copyright © 2004, Benjamin Cummings.]

The composition of human hemoglobin is different during development:
in the given developmental stages hemoglobin is composed of different subunits.
Subunits are encoded by the globin genes.



Methylation of globin genes in human embryonic blood cells



Inactive globin genes, which are not expressed in a given developmental stage, display methylated cytosines in their promoter.
Thus, **promoter methylation** is one way to inactivate genes.