REGULATION OF GENE EXPRESSION

THE REGULATION OF GENE EXPRESSION IN EUKARYOTES

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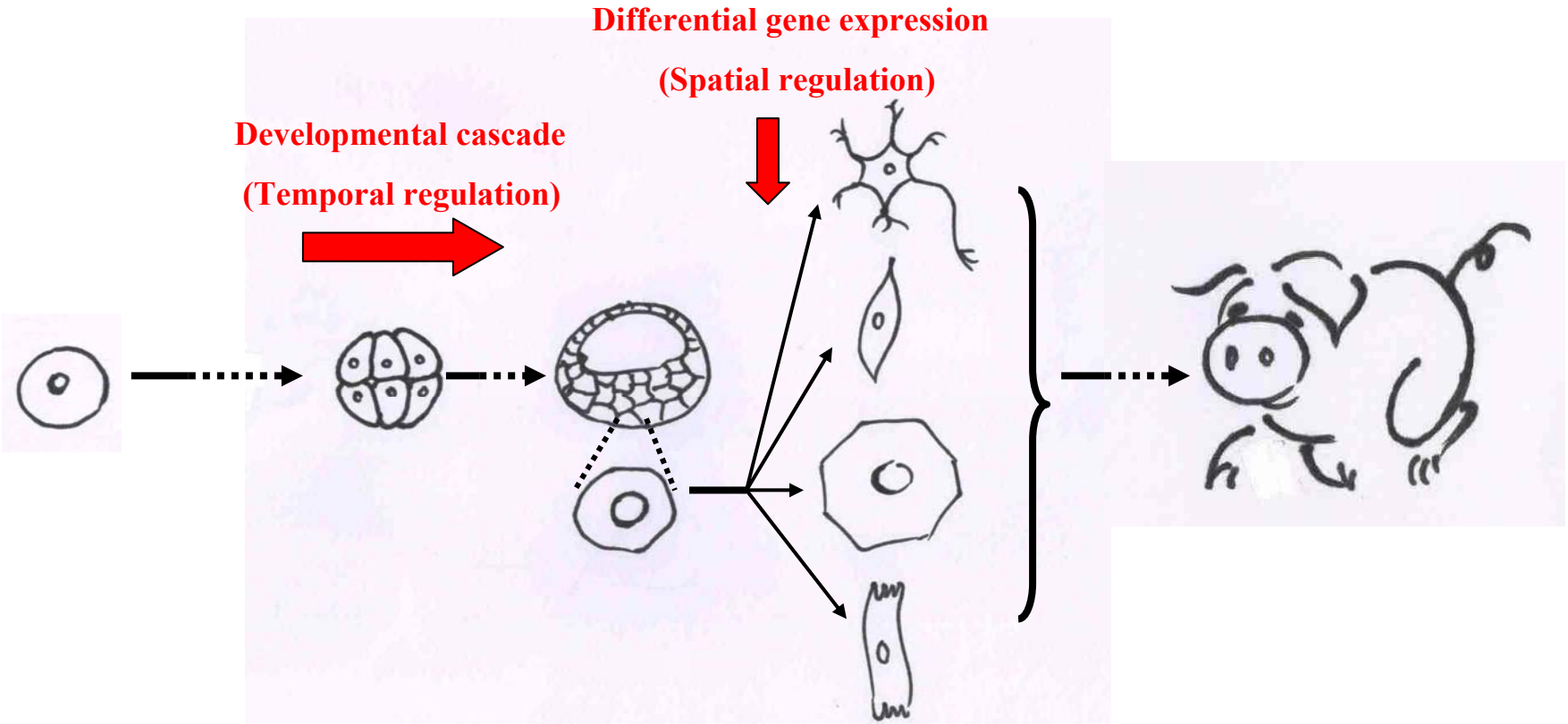
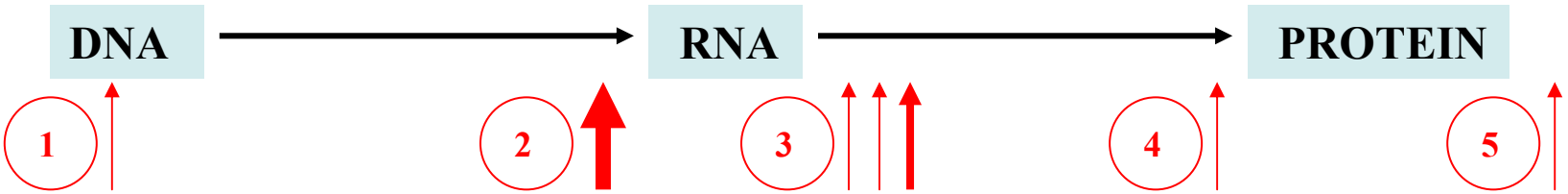


The organizational structure of an eukaryotic cell determines the mode of gene regulation :

- **Chromatin packaging into nucleosomes and other organized structures → possible control at the chromatin structure level**
- **Compartmentalization of the cell → need of internal signaling system to communicate between different compartments**
- **Multicellular organism → need of intercellular communication system**
- **Differentiation of a totipotent cell into different cell types during body formation → spatial and temporal regulation**

CONTROL LEVELS OF GENE EXPRESSION IN EUKARYOTES



1. ***Control at the level of chromatin and genome structure***
2. ***Control at the level of transcription initiation***
3. ***Control at the level of post-transcription initiation including transcription elongation, mRNA stability, alternative splicing***
4. ***Translational control***
5. ***Post-translational control***

- **Due to organizational characteristics of eukaryotic cell and organism, and the spatial and temporal separation of transcription and translation, the regulation of gene expression in eukaryotes can be exerted at more levels than in prokaryotes,.**
- **Nevertheless, the predominant control level of gene expression is at transcription initiation as found in prokaryotes**

CONTROL AT THE LEVEL OF CHROMATIN AND GENOME STRUCTURE

EPIGENETIC INHERITANCE

Chromatin structure and organization fundamentally affect gene expression by changing the chromatin structure, especially its compaction state. The degree of chromatin compaction essentially relies on histone modifications and DNA methylation. Active chromatin regions usually contain high rate of acetylated histones and unmethylated DNA whereas inactive regions are associated with nonacetylated histones and methylated DNA.

Histone modifications and DNA methylation constitute the base of a special mechanism of gene expression control called epigenetic inheritance. Epigenetic inheritance refers to inherited gene expression pattern independent of modifications in DNA sequence. It concerns alternative heritable expression of genes that occur throughout the whole life of an organism and usually expand to its offspring. Epigenetic inheritance is essential to the normal development of eukaryotes.

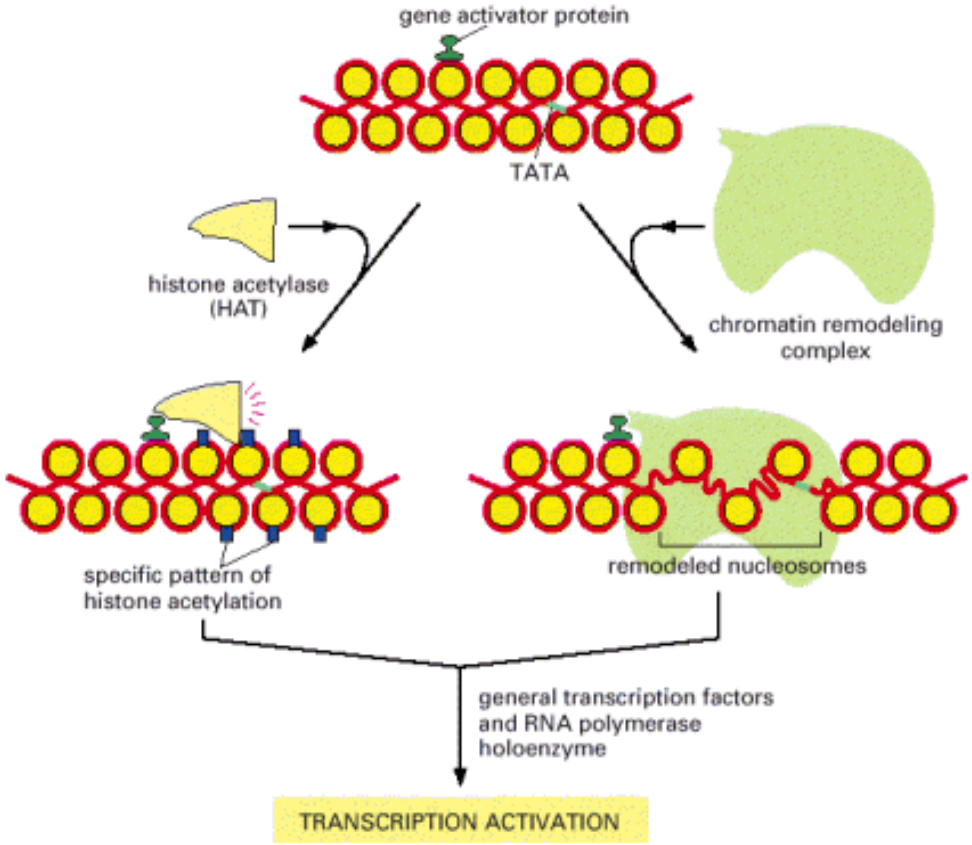
Some phenomena considered as epigenetic regulation involve X chromosome inactivation and genomic imprinting. Epigenetic inheritance is crucial for normal embryonic development, plays important roles in cancerogenesis and other biological processes.

What distinguish epigenetic control from the gene expression programs of an organism ?

➜ In metazoa, the expression or lack of expression of tissue-specific genes in certain cell types, although maintained throughout cell generations, does not belong to epigenetic inheritance. It is a part of an innate predetermined genetic program, unchanged for all individuals of the species. Normally, both alleles are active.

➜ Epigenetic inheritance, in contrast, do not depend on a predetermined genetic developmental program. It can be affected by environmental conditions and individual genetic polymorphisms, and when established, becomes stable throughout the lineage. Only maternal or paternal copy of the gene is active

HISTONE MODIFICATIONS



For gene expression, eukaryotic DNA must be decompacted to become accessible to transcription initiators. The decompaction process is ensured by nucleosome modifiers.

Nucleosome modifiers are classified into two groups :

1. Enzymes that modify the amino-terminal tails of histones such as histone deacetylases, histone acetylases and histone methyltransferases

2. Remodeler complexes that "loosen" the interaction between DNA and histones

Modifications of the chromatin can activate gene expression by two ways :

1. "Loosening" the chromatin structure, thus liberating binding sites for regulatory proteins

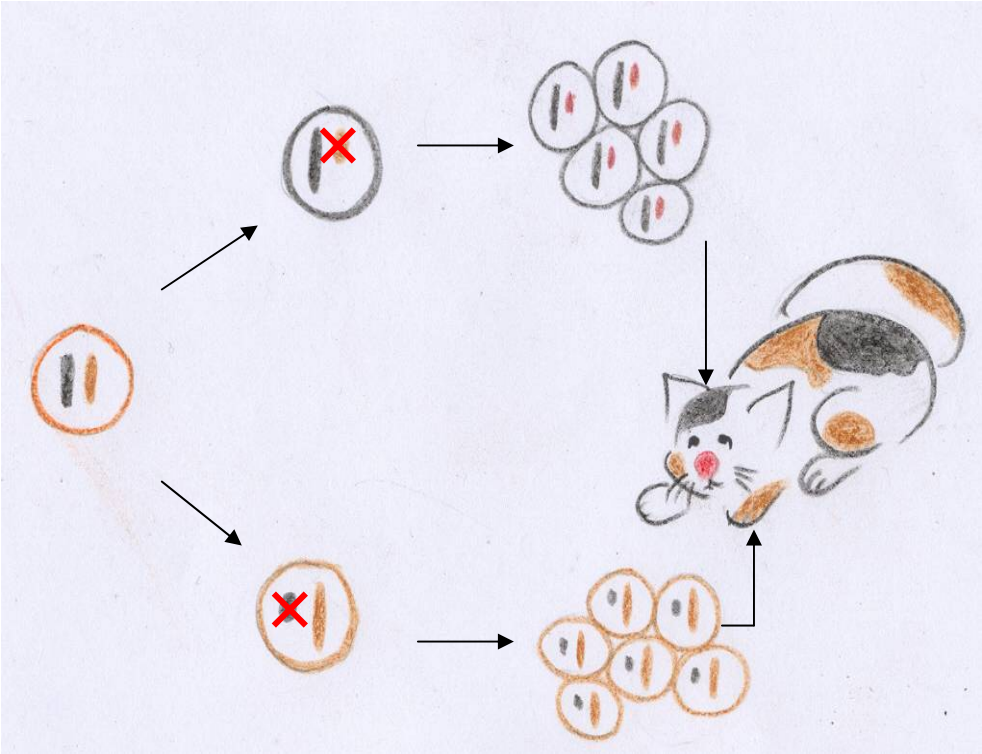
2. Enhancing the binding of some particular regulatory proteins to the modified chromatin

An well-known example of epigenetic control through chromatin compaction modification is the X-inactivation.

X-INACTIVATION

In female mammals, one X chromosome of the sexual chromosome pair XX is randomly inactivated at a very early stage of the embryogenesis. This phenomenon is called X- inactivation or Lyonization (from the name of Mary Lyon who postulated the theory). The chromatin compaction spreads over the whole chromosome and inactivates it. The cell containing one inactivated X chromosome gives rise to a lineage bearing the active X chromosome of the same parental origin.

A well-known example of X inactivation concerns the calico cat's fur. Calico cats are mostly female.



Colour patches of the fur are due to the random inactivation of one X chromosome of the pair bearing "black"/"brown" alleles.

X-inactivation occurs as follows :

***XIST* gene, situated on the X chromosomes, encodes a non-translated RNA. On one X chromosome, *XIST* gene is transcribed into many RNA molecules that coat the chromosome and inactivate it. On the other chromosome, *XIST* gene is inactivated by DNA methylation, thus the X chromosome remains active.**

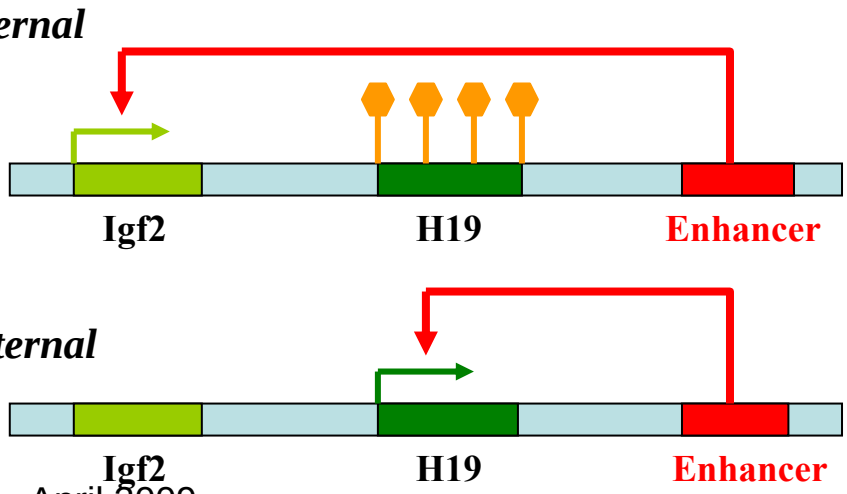
GENE SILENCING BY DNA METHYLATION

In mammals, the cytosine belonging to the structure 5' mC p G 3' can be methylated
3' G p Cm 5'

DNA methylation prevents the binding of the transcriptional machinery and is associated with transcriptional silencing.

DNA methylation.is the underlying mechanism of a genetic process called imprinting which is considered as an epigenetic inheritance. In a diploid cell, a gene exists in two copies located in two homologous chromosomes, one inherited from the father, the other from the mother, both are equally expressed. However, for an imprinted gene, the expressed allele is determined by its parental origin. Imprinted genes account for about 1% of mammal genomes.

Alleles of imprinted genes are selectively inactivated in the developing germ cells - sperm or oocyte. This inactivated state of maternal or paternal allele is maintained throughout embryonic development.



"Adapted from Watson J.D. et al. 2004. Molecular Biology of the Gene. 5th edition, p.560, fig 17.25. Benjamin Cummings., CSHL Press"

A well-studied imprinting phenomenon involve *H*19 and *Igf*2 genes closely linked in human chromosome 11. They compete for common enhancer element to be expressed. Methylation of paternal *H*19 abolishes enhancer effect thus prevent paternal *H*19 expression while allows the expression of paternal *Igf*2. On the other hand, unmethylated maternal *H*19 gains enhancer effect and is transcribed. Thus, *Igf*2 gene is paternally expressed whereas *H*19 gene is maternally expressed

BIOLOGICAL MEANINGS OF EPIGENETIC INHERITANCE

Iraq horse breeders in the ancient times observed that offsprings of a male horse and a female donkey are different from those originated from a crossing between male donkey and female horse.

Epigenetic inheritance play crucial roles in normal growth and development of multicellular eukaryotic organisms :

ᔓ In embryonic development, epigenetic abnormalities can lead to genetic disorders such as Prader-Willi and Angelman syndromes. Babies with Prader-Willi and Angelman syndromes are born with both alleles expressed, an abnormal active paternal allele (Prader-Willi) or an abnormal active maternal allele (Angelman) of the same gene.

In Assisted Reproductive Technologies, epigenetic inheritance is thought to be associated with abnormal embryonic development due to loss of maternal/paternal selective allele expression and high rate of embryonic losses.

It is thought that imprinting is a tentative of the mother to protect herself from her fetus. Silencing of maternal alleles limit the fetus growth.

ᔓ DNA hypermethylation cause tumor suppressot gene silencing whereas DNA hypomethylation favorize oncogene expression. These are the cause of many cancer types, e.g the aberrant methylation pattern of *Igf*2 and *H*19 genes give rise to simultaneous expression of maternal and paternal alleles and are the cause of many human cancers.

Demethylating agents and agents promoting histone acetylation constitute possible therapeutic approaches for certain cancers.

ᔓ Epigenetic control is thought to be used by cells to silencing some regions in the genome containing repetitive "useless" DNA, e.g inserted "foreign" (viral) sequences (transposon). Most of these transposons are methylated

GENE HYPERACTIVATION BY AMPLIFICATION

A totally opposite process, called gene amplification, leads to the production of many copies of the genes located in a special region of the chromosome. Each copy can be transcribed and translated, leading to an overproduction of the corresponding protein.

This phenomenon occurs in normal cell growth in some species as well as in abnormal cell growth such as in some cancerous conditions

ᔓ In normal cell growth : (1) In the amphibian *Xenopus laevis*, rDNA gene number is amplified 2500 times during oogenesis to respond to great protein synthesis needs, the amplified rDNA exists in the form of extrachromosomal circular DNA and is replicated by rolling circle DNA replication, (2) In *Drosophila*, chorion genes – chorion is the eggshell surrounding mature oocyte – are amplified in the ovarian follicle cells.

ᔓ Genes are amplified in some special conditions. In yeast, cells selected for copper resistance have increased copies of a gene, CUP1, encoding the Copper Binding Protein Chelatin, arranged in tandem arrays of about 12 copies. In cancerology, overexpression of oncogenes through gene amplification leads to deregulated cell growth, e.g amplification of the myc oncogene is observed in a wide range of tumors, ErbB-2 in breast tumor and HER-2/neu in ovarian cancer. Furthermore, gene amplification can result in drug resistance in cancer treatment. In some multidrug-resistant malignant cell lines, a gene called *mdr* which encodes proteins acting as cytoplasmic membrane pump is amplified. The overproduction of MDR proteins causes ejection of chemotherapy drugs out of the cell, rendering the drugs inefficient. These amplified genes form double-minute chromosomes composed of small circular DNA generated from contiguous chromosomal regions.

CONTROL AT THE LEVEL OF TRANSCRIPTION INITIATION

CONTROL OF TRANSCRIPTION INITIATION

As in prokaryotes, the control of transcription initiation is also the predominant control level of gene expression in eukaryotes. This control is realized through binding of TRANS proteins to CIS sequences.

1. TRANS proteins are all the proteins involved in the control of transcription. These TRANS factors can be classified into two main classes :

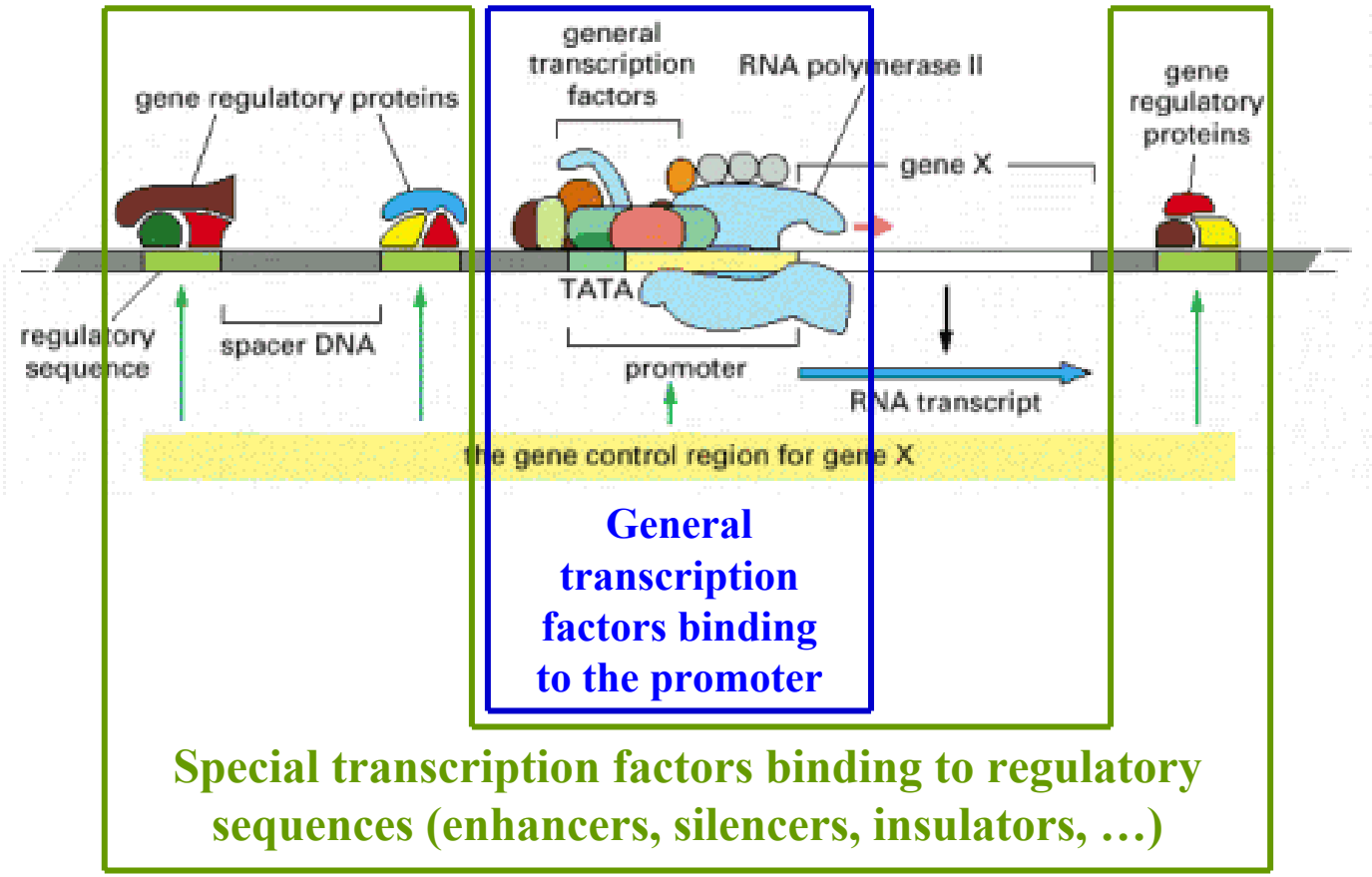
- **The general (basal) transcription factors are presented in "Transcription"**
- **The special transcription factors will be detailed in this lecture**

2. CIS elements include all the DNA sequences involved in the control of transcription

- **Promoter sequences**
- **Regulatory sequences including enhancers, silencers, insulators**

Promoter differ from enhancer/silencer by some features. Promoter has to be placed upstream of and adjacent to the coding region whereas enhancer/silencer can exert their activities upstream, downstream of or inside a gene, at any orientation and also at distance.

GENERAL/SPECIAL TRANSCRIPTION FACTORS



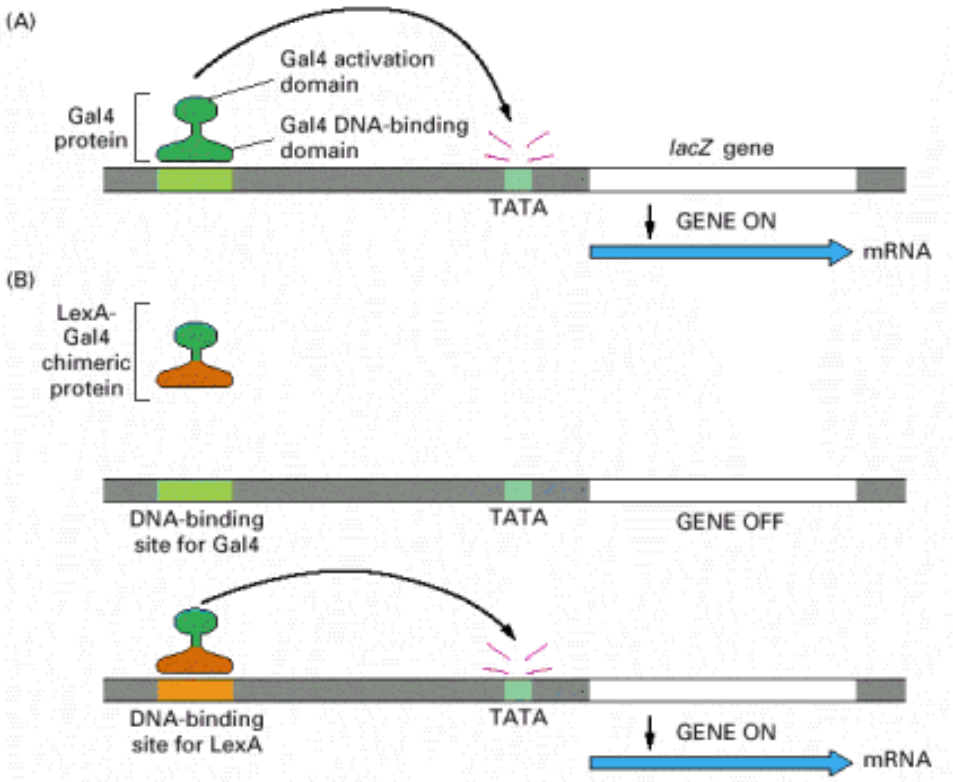
General (basal) transcription factors are necessary to initiate transcription at one promoter

Question :" WHAT DECIDES WHICH PROMOTER WILL BE ACTIVATED AT ONE TIME AND ONE PLACE ?"

Answer : "IT IS THE SPECIAL TRANSCRIPTION FACTORS WHICH ARE TIME OR TISSUE-SPECIFIC OR ACTING UNDER SPECIAL PHYSIOLOGICAL CONDITIONS"

TRANSCRIPTIONAL FACTORS ARE MODULAR

Eukaryotic transcriptional factors have modular structure, like some regulatory proteins in prokaryotes. Functional modules of eukaryotic regulatory proteins are usually located in different domains of the macromolecule



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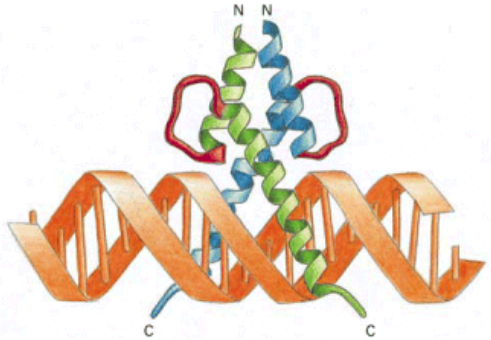
An experiment showing the modular structure of the yeast activator protein Gal4. (A) The normal activation of gene transcription produced by the Gal4 protein. (B) By gene fusion techniques, a hybrid activator can be created by combining the Gal4 activation domain with the LexA DNA-binding domain from a bacterial regulatory protein. The hybrid activator has no effect unless a DNA-binding site specifically recognizing the LexA DN-biding domain is inserted into the experimental system.

In this experiment, the *E. coli lacZ* gene, which codes for the enzyme β-galactosidase, is used as a reporter gene to express the effect of regulatory elements.

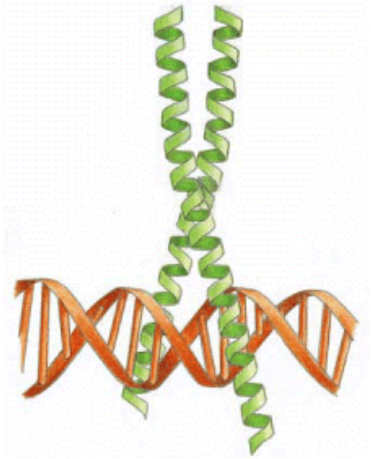
TRANSCRIPTIONAL FACTOR STRUCTURE



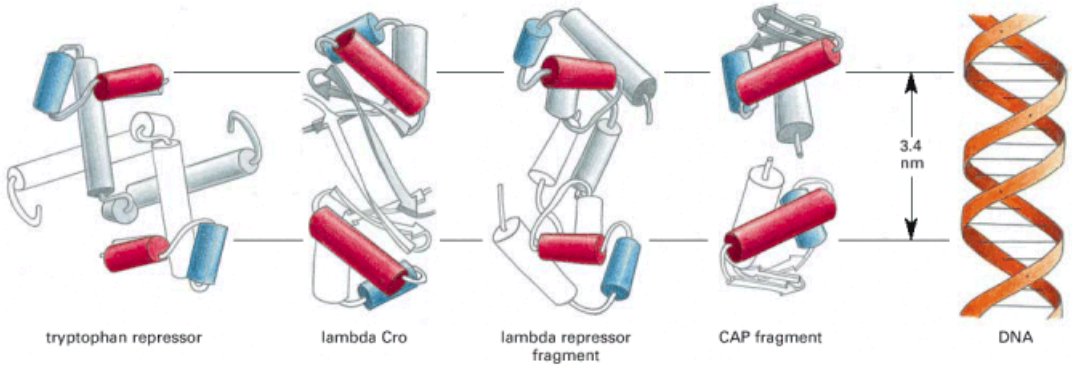
"Helix-Loop-Helix" DBD

TRANS proteins are composed of many domains. DNA-binding and activation domain are the two common domains to all TRANS elements. Other domains can be present such as Ligand-binding, Dimerization or Repressor domain.

- **DNA-Binding Domain (DBD) : The most common motifs of DNA-binding domain include "helix-turn-helix", "zinc finger",**
- **Dimerization domain includes some motifs such as "leucine zipper", "helix-loop-helix".**
- **Transcription activation domain :**



"Leucine zipper" DBD



"Helix-Turn-Helix" DBD

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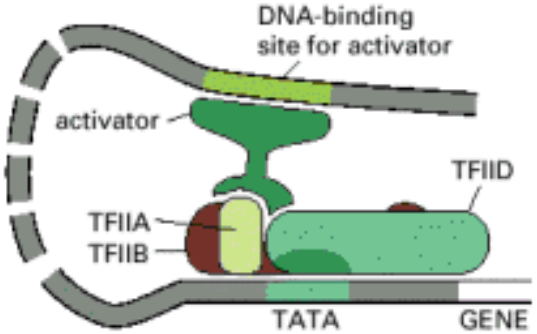
TRANSCRIPTIONAL FACTORS CAN ACT AT DISTANCE

The action at distance of transcriptional factors involve the participation of : (1) "architectural" proteins which bend a DNA region to bring all the regulatory elements close together and, (2) insulators which prevent the random activation of promoters situated over a large distance between an enhancer and its regulated promoter.



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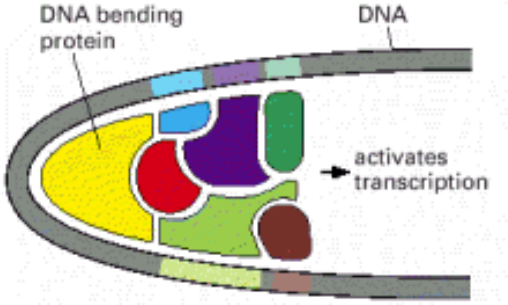
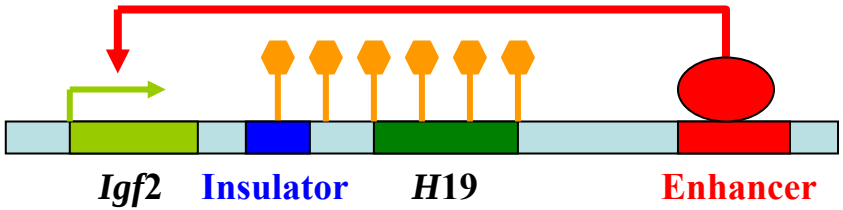
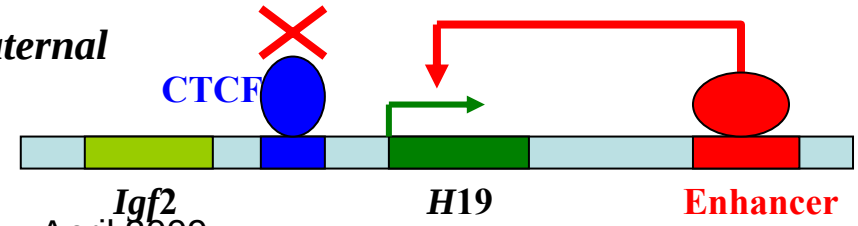


Examples of DNA-bending proteins

Paternal



Maternal



"Adapted from Watson J.D. et al. 2004. Molecular Biology of the Gene. 5th edition, p.560, fig 17.25. Benjamin Cummings., CSHL Press"

The role of insulators can be illustrated by the regulation of *Igf*2 and *H*19 gene expression. A regulatory protein, CTCF, binds to the insulator sequence of the maternal chromosome, thus inhibiting the enhancer effect on *Igf*2. *H*19 can then be activated. On the paternal chromosome, the insulator sequence as well as H19 gene are methylated, preventing CTCF binding, thus favorizing the activation of *Igf*2 gene

CONTROL AT THE LEVEL OF POST-TRANSCRIPTION INITIATION INCLUDING TRANSCRIPTION ELONGATION, mRNA STABILITY, ALTERNATIVE SPLICING

POST-TRANSCRIPTION INITIATION CONTROL

The post-transcription initiation control include the control of transcription elongation, the control of mRNA stability, and most importantly the alternative splicing.

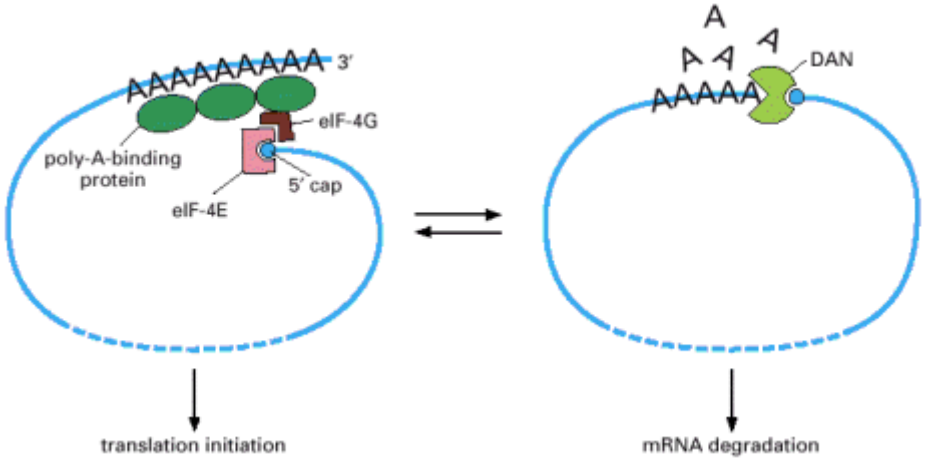
CONTROL OF TRANSCRIPTION ELONGATION

Transcription elongation rate is not always constant. In many genes, RNA polymerase can pause during the elongation step. Pausing is influenced by the intracellular NTP concentration, the presence of some transcription elongation factors and the secondary structure of the growing transcript.

In some cases, the paused RNA polymerase can be put back in movement by activators, e.g in *Drosophila*, the *HSP70* gene expression is controlled by two activators, the first one initiates its transcription. During elongation, the RNA polymerase stalls at a certain distancefrom the promoter. When heat shock occurs, the second activator, HSF, binds to a region at the promoter and recruits a kinase, P-TEF, which phosphorylates the RNA polymerase CTD and liberates it from its stalled status

Another example concerns the expression of HIV genes. A viral activator called Tat binds to a region called TAR which exists in the form of a stem-loop structure at the 5'UTR region of all HIV RNAs. In the absence of Tat, RNA polymerase stalls causing premature transcription termination. When present, Tat binds to TAR in one transcript, loops backward and interacts with the transcription initiation complex assembled at the promoter. This interaction phosphorylates the polymerase CTD leading to enhanced processivity of RNA polymerase which can correctly terminate all transcripts.

CONTROL OF mRNA STABILITY



Messenger RNAs, exported from the nucleus to the cytoplasm, are translated until they are degraded. Long-lived mRNAs give rise to more polypeptides than short-lived mRNAs. Thus, mRNA life time is another control point of gene expression.

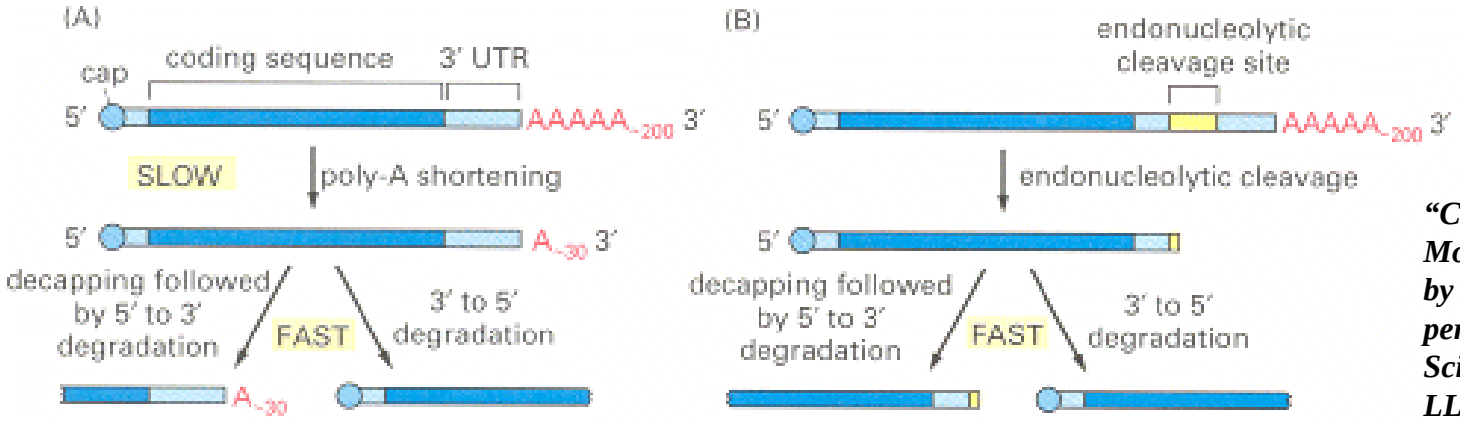
Actually, mRNA stability is one determinant of the efficiency of gene expression. In fact, since the translational machinery as well as mRNA degradation by deanylation are closely associated with both the 5'cap and the poly-A tail, translation initiation competes with mRNA degradation. The efficiency of mRNA use results from this competition.

In the figure above, an enzyme called DAN which cleaves the poly-A tail is associated with the 5'cap. Thus,

CONTROL OF mRNA STABILITY

The longevity of mRNA is influenced by some factors :

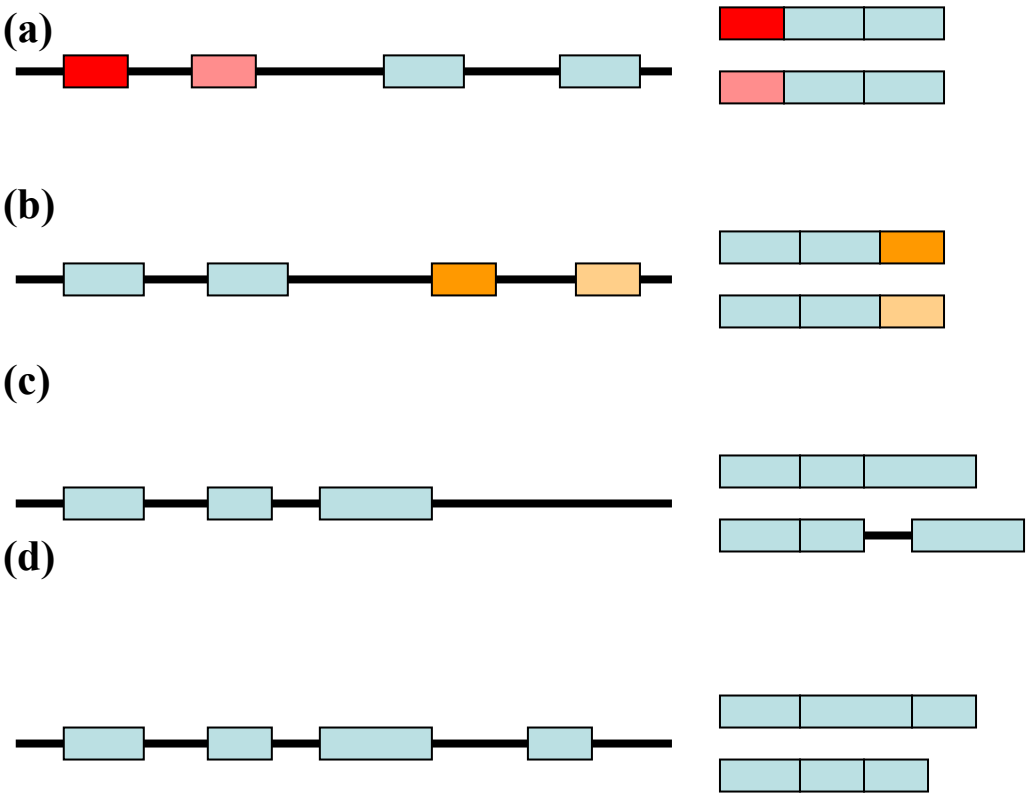
- **The poly-A tail length enhances the mRNA life time, for example histone mRNAs lack poly-A tail and have very short life time**
- **The sequence of the 3'UTR preceding the poly-A tail also affects mRNA stability. Some short-lived mRNAs have many repeated sequences AUUUA in this region.**
- **The concentration of some metabolites, such as hormones, can also influence mRNAs longevity.**
- **The decapping process accelerates mRNA degradation**



In the figure above, mRNA degradation occurs in a deanylation-dependent manner (A) or –independent manner (B) due to the existence of a internal endonucleolytic site. Even if 5'-3' and 3'-5' degradation are separately presented, an mRNA undergoes simultaneous degradation processes.

ALTERNATIVE SPLICING

RNA splicing is one of the RNA processing pathways leading to introns removal and exons splicing of a pre-mRNA. In some cases, introns removal and exons splicing can be done in different ways leading to the formation of different mRNAs from an mRNA precursor, this phenomenon is called alternative splicing. There are four common modes of alternative splicing :



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(a) Alternative use of the promoters. Depending on the use of the upstream or downstream promoter, the first or the second exon will be retained in the mature mRNA.

(b) Alternative use of the poly-A sites determines the retention of the 3'end exon or the previous exon

(c) Intron retention. This mode of alternative splicing can have striking effect if the retained intron contains a stop codon. This will give rise to a truncated protein when the mRNA is translated

(d) Alternative splicing of internal exons. This gives rise to different mRNAs which encode different polypeptides with similar or totally different functions.

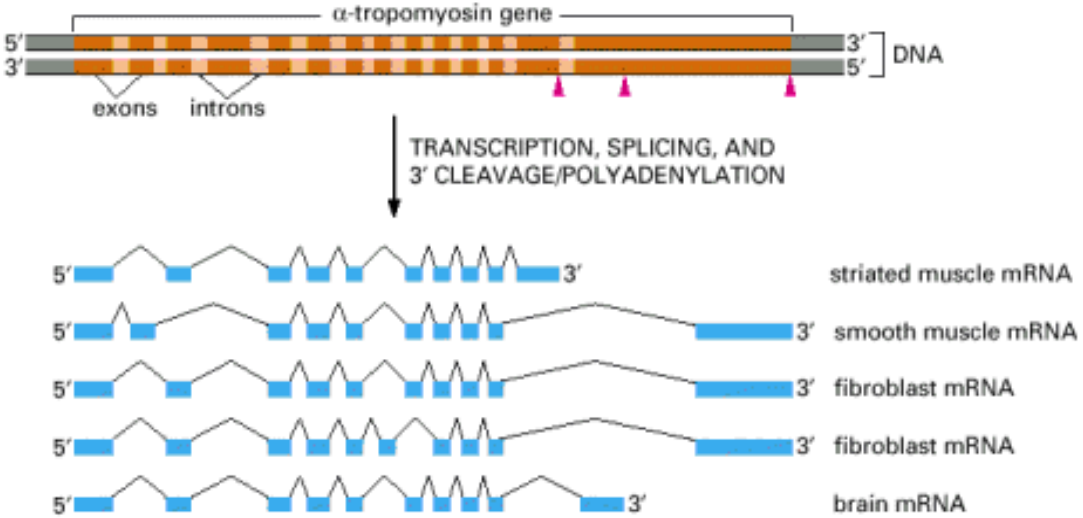
ALTERNATIVE RNA SPLICING

The number of potential different proteins generated from one gene, in extreme case, such as for the DSCAM gene in *Drosophila*, can rise to thousands !

The question is : "There are mechanisms to guarantee the precision of RNA splicing, so how can alternative splicing occur as a common biological event ?"

➔ In cases where alternative splicing occurs, there are existence of special activators and repressors. They are called splicing enhancers/silencers and direct the splicing machinery to selected exon-intron boundaries.

These regulatory proteins can act in a developmental stage-dependent manner, e.g the alternative splicing of a cascade of genes involved in sex determination in *Drosophila*. During embryogenesis, activators induce alternative splicing of *Sxl* gene ; the products of this alternative splicing differentially regulate splicing pattern of *tra* gene, which in its turn influences the alternative splicing of *dsx* gene. Different versions of Dsx proteins can repress or activate male or female genes leading to male/female development.

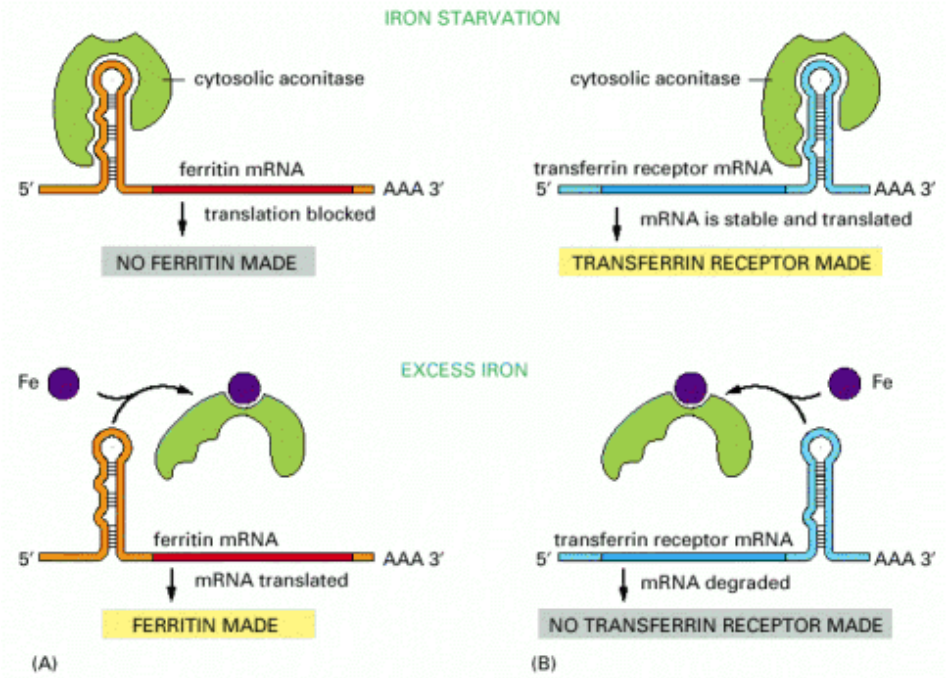


Splicing regulatory proteins can usally act in a tissue-dependent manner, e.g in α-tropomyosin gene (picture). In this case, tissue-specific factors determine the splicing pattern by choosing the 5'splice sites and 3'splice sites to be used.

TRANSLATIONAL AND POST-TRANSLATIONAL CONTROL

TRANSLATIONAL CONTROL

ᔓ A known example of translational control concerns proteins involved in iron metabolism. Ferritin has a function in iron storage whereas transferrin receptor is responsible of iron import into the cell. When cytosolic concentration of iron increases, the synthesis of ferritin increases in order to bind the extra iron (A) whereas the synthesis of transferrin receptors decreases in order to import less iron across the plasma membrane (B).



Both translational process are regulated by one regulatory protein, aconitase, which can bind iron. Aconitase can recognize and binds to a stem-loop structure at the 5' UTR of ferritin mRNA. This binding blocks translation initiation of ferritin mRNA. Aconitase can also binds to a similar stem-loop structure located at the 3' UTR of transferrin receptor mRNA. This binding enhances mRNA stability. Aconitase dissociates from the mRNA when it binds iron. Thus, when iron concentration rises, translation of ferritin mRNA is initiated whereas transferrin receptor mRNAs are rapidly degraded.

TRANSLATIONAL CONTROL

ᘓ The expression of Gcn4, a yeast transcriptional activator, is regulated at translational level. The Gcn4 mRNA contains 4 additional small ORFs (open reading frames) located upstream of the coding sequence.

The first ORF is preferentially translated and once translation finished, the 40S ribosome subunit remains bound to the RNA and begins the scanning process. It has to associate with the eIF2-tRNA^{Met} to be able to initiate translation of the downstream ORFs.

When amino acids are scarce, available eIF2-tRNA^{Met} decreases → ribosome can not recruit eIF2-tRNA^{Met} before it reaches the Gcn4 ORF. Thus Gcn4 protein is synthesized. Under abundant amino acid conditions, ribosome rapidly associates with eIF2-tRNA^{Met} and continue to initiate the three successive small ORFs. After translating all these small ORFs, the ribosome dissociates from the RNA and will not translate Gcn4 ORF.

ᘓ The inactivation of eIF2 through its phosphorylation is another mechanism of translational control.

An example concerns translational control exerted by heme. Heme activates a protein kinase called HCI (heme controlled inhibitor) which phosphorylates eIF2. As we know, eIF2/GTP brings the the initiator tRNA ^{Met} to the ribosome, becomes eIF2/GDP and is reactivated through GTP/GDP exchange. The phosphorylated inactive eIF2/GDP can not be regenerated → translation initiation is inhibited

POST-TRANSLATIONAL CONTROL

Post-translational control of gene expression can be defined as a regulation process in which protein structure, and thus function, are modified after translation.

These modifications involve chemical modifications of amino acids, alteration of the order od amino acids in the polypeptide backbone and others.

- **The most common chemical modifications of amino acids include phosphorylation, glycosylation and ubiquitination. Phosphorylation is the addition of phosphate to an amino acid side chain. Phosphorylation alters protein function and is usually associated with activation. In glycosylation, one or more sugars are added to amino acid side chain. Glycosylation can change protein solubility, folding characteristics or targeting to a particular cell region. Ubiquitination is the first step in protein degradation process. When a protein is bound by ubiquitins, it will be directed to the proteasome to be degraded.**

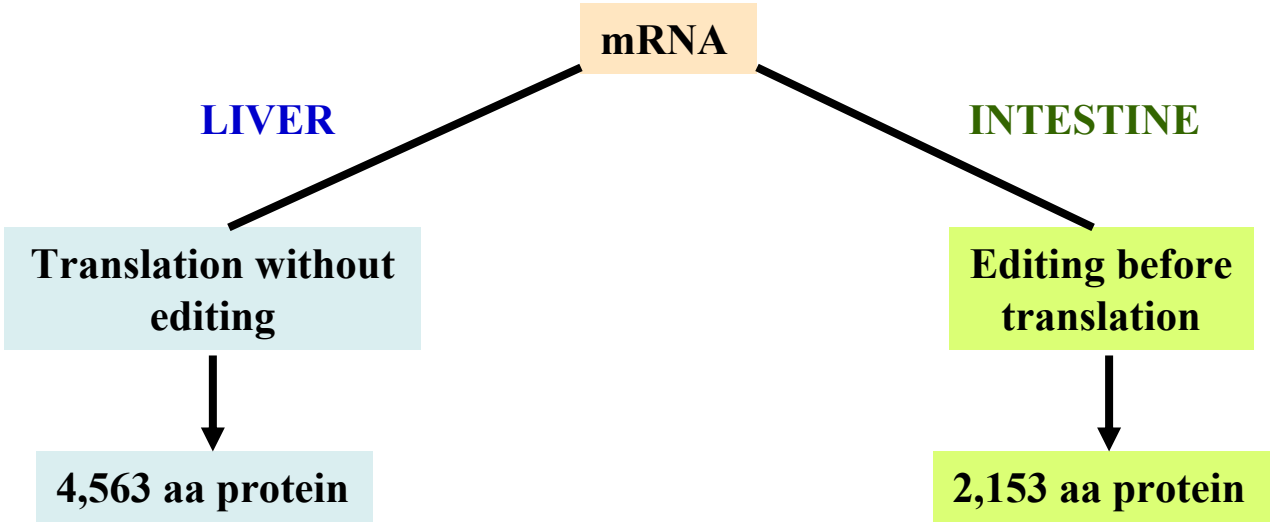
- **The polypeptide backbone itself can be altered. The most known examples concern some large protein precursors which are cleaved after translation to give rise to active forms, e.g insulin, trypsin, …**

An interesting types of proteins called inteins can direct their own excision and the ligation of flanking polypetide fragments which are called exteins. It is not clear if inteins have role in the regulation of gene expression, but proteins related to inteins called hedgehog proteins are involved in embryonis development.

RNA EDITING

RNA editing is a process in which the RNA sequence is modified. The two editing mechanisms include : site-specific deamination and guide RNA-directed insertion of uridine.

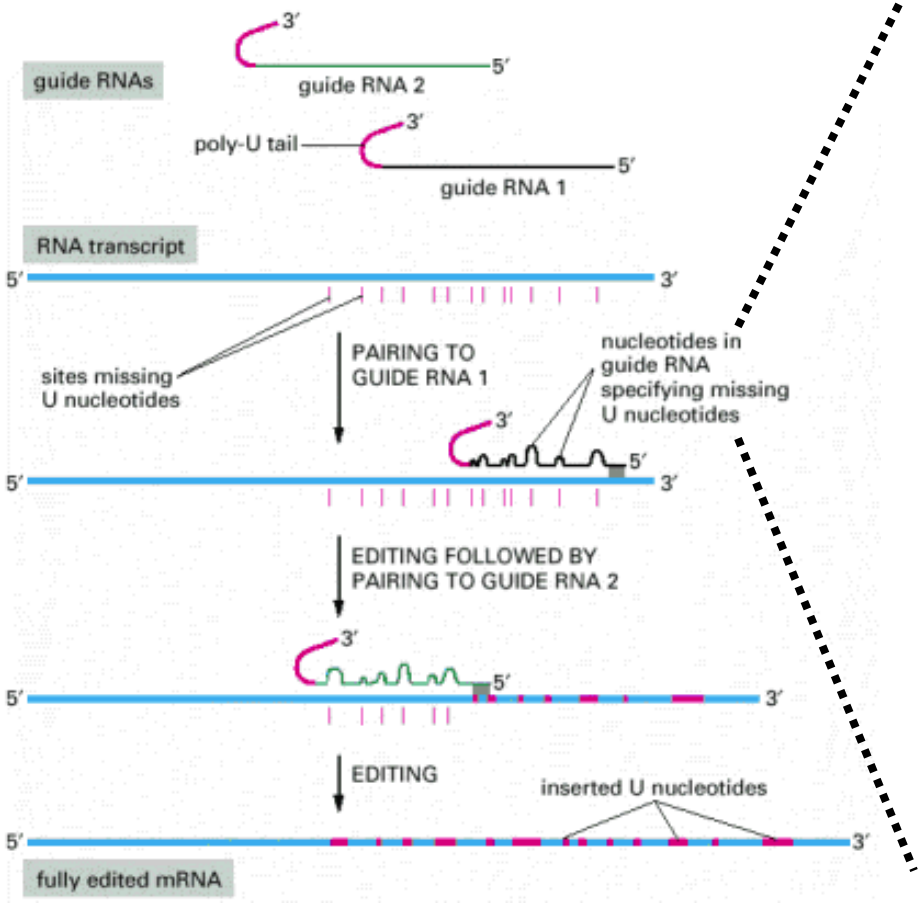
ᔓ Site-specific deamination : a cytosine residue within the RNA is changed into uridine by deamination. A well known example concerns the mammalian apolipoprotein-B gene. Transcription with and without RNA editing in this case gives rise to two tissue-specific proteins



In other cases, adenosine can be deaminated to produce inosine. Since inosine can basepair with cytosine, this induces point mutation which alter the protein sequence.

RNA EDITING (continued)

Guide RNA (gRNA)-directed insertion of uridine : many Us are inserted into the transcripts as found in the mitochondrial mRNA of trypanosomes. These insertions completely shift the reading frame and give rise to totally different proteins.



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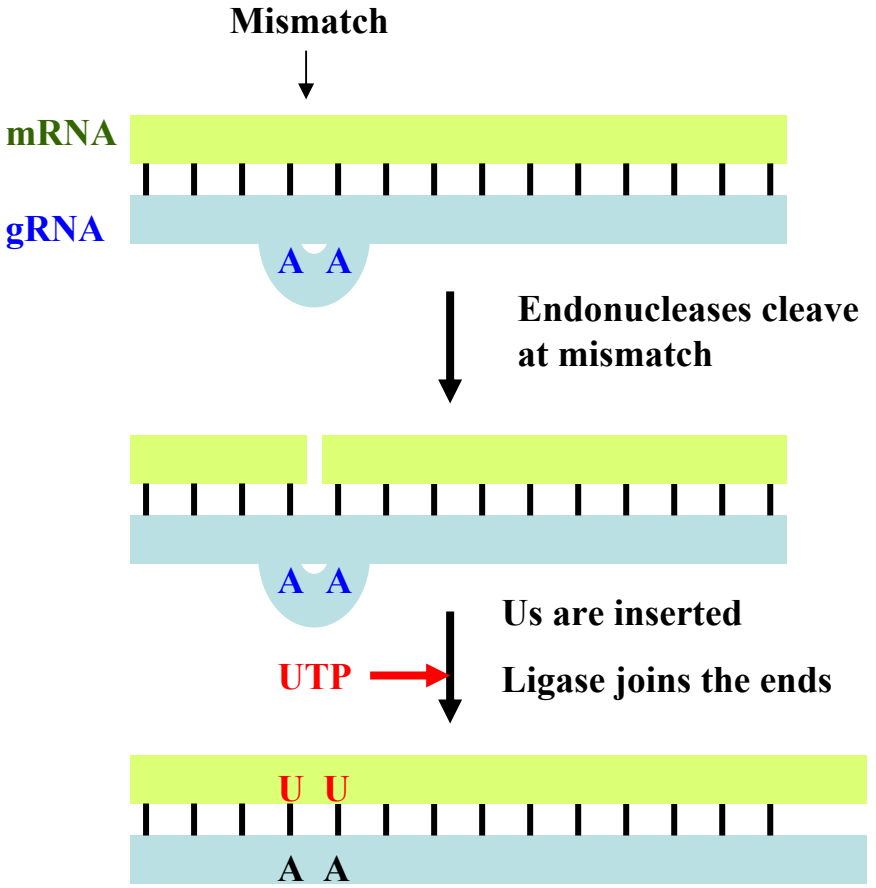


"Adapted from Watson J.D. et al. 2004. Molecular Biology of the Gene. 5th edition, p.405, fig 13.26. Benjamin Cummings., CSHL Press"

REGULATION OF GENE EXPRESSION BY RNAs

The expression of some genes are regulated by RNA rather than by proteins. An example is the attenuation regulation of *E. coli* trp genes. Riboswitches which are regulatory RNA elements work in a similar way, through their alternative secondary structures. RNAs can regulate gene expression in many ways :

- **Short RNAs can repress gene expression by a process called RNA interference (RNAi). RNAi can intervene at transcriptional or translational level and mRNA stability. RNAi has diverse biological functions ; it can affect development, e. g in the worm *C. elegans*, or can be used by plants to avoid viral infection. These short RNAs, of about 23 bp long, are the products of long dsRNAs which are cleaved by the nuclease Dicer. These siRNAs (short interfering RNAs) direct a nuclease complex called RISC (RN-induced silencing complex) to the repression of gene expression by three ways : (1) destroy mRNAs having complementary sequence with the siRNA, (2) inhibit the translation of the complementary mRNAs, (3) induce chromatin modification within the promoter of these homologous genes leading to their silencing.**

- **MicroRNAs (miRNAs) is another class of regulatory RNAs. They are about 21-22 nucleotides long and are produced from the digestion of larger transcripts by Dicer. miRNAs can also destroy or inhibit the translation of target mRNAs which have homology to the miRNAs.**

There are hundred of genes encoding these miRNA in some eukaryotes ; most of them are involved in developmental regulation

siRNAs and miRNAs are actively used by scientists to silence target genes.

SUMMARY

The regulation of gene expression in eukaryotes is crucial for an essentially muticellular organism to develop harmoniously according to a pre-determined genetic program. In this case, the regulation is not rapid nor synchronized for a group of genes but precise for each individual gene.

The eukaryotic cell structure provides possible control for gene expression at many levels : chromatin structure, transcription initiation and post-initiation, translation and post-translation.

At the chromatin structure level, genes can be silenced by changing the degree of compacting or by chemical modifications of the DNA. Genes can also be hyperactivated through amplification. Proteins participating in the changement of chromatin structure are called nucleosome modifiers.

Epigenetic inheritance is a gene expression control relying on control of chromatin structure independent of any DNA sequence changes. Epigenetic inheritance is mainly based on histone modifications and DNA methylation. Epigenetic regulations include X-inactivation and parental imprinting which is crucial for normal embryonic development. Abnormal epigenetic inheritance can cause cancers and many genetic disorders.

Transcription initiation is the most important level of gene expression control in eukaryotes as in prokaryotes. Besides the general transcription factors necessary for RNA polymerase synthesis activities, there are special transcription factors which are required for correct spatial and temporal development of the organism or for response to particular conditions. These special transcription factors are modulars, they are composed of some domains, especially DNA binding and activation domains. They can act at distance to enhance or silence gene expression.

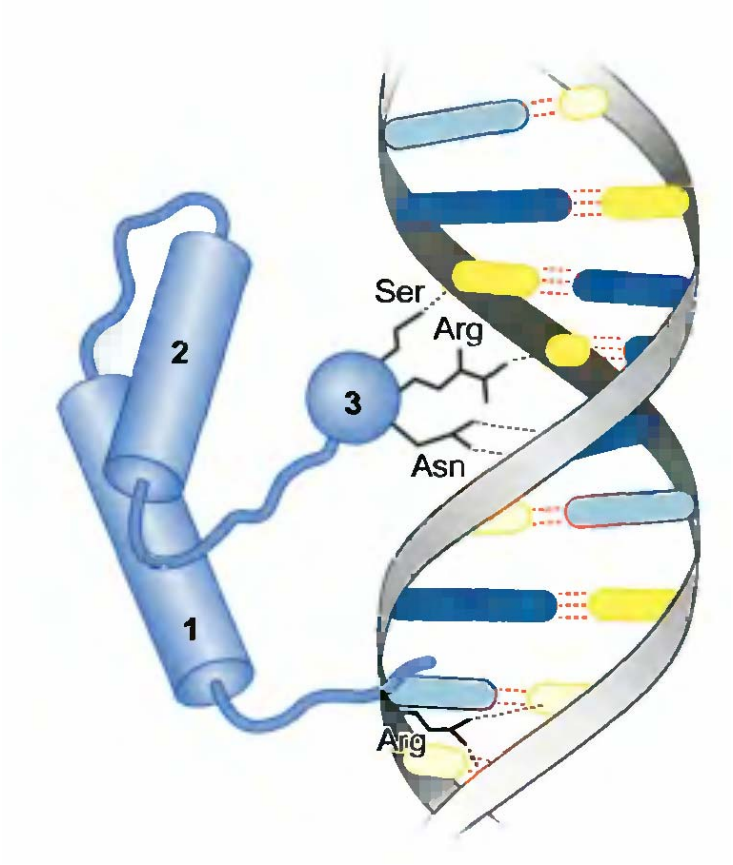
SUMMARY (continued)

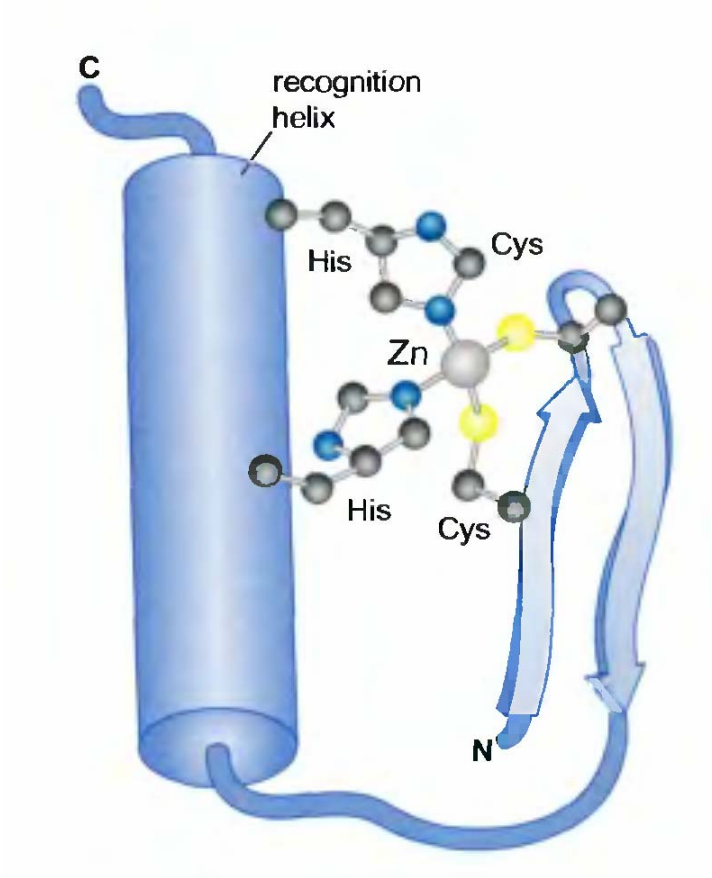
After transcription has been initiated, gene expression can be controlled at the elongation step, or through mRNA stability and most importantly, through alternative splicing. Alternative splicing can give rise to different mRNAs, and thus different proteins from one single gene.

Translational control and post-translational control are additional control levels found in a few cases

RNA editing is a particular form of structure modifications of the RNA. These modifications especially involve frameshift mutations in the transcripts leading to the formation of totally different proteins form one mRNA.

Finally, gene expression can be controlled, not by proteins, but by RNAs, especially siRNAs (short interfering RNA) or miRNAs (microRNA). Their actions are varied, inhibiting transcription or translation, inducing RNA degradation or chromatin modification.


Ser
Arg
2
3
Asn
1
Arg


C
recognition
helix
His
Cys
Zn
His
Cys
N