Genética y genómica de las hipercolesterolemia

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RAMCV

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Sinopsis

Conceptos básicos de Biología molecular

Biología del Colesterol

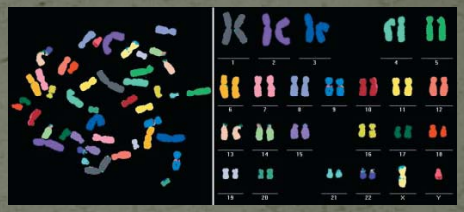
Genética y genómica

Nuevas terapias de base Genética

Definiciones

Genética:

Es el campo de la biología que busca comprender la herencia biológica que se transmite de generación en generación.



Genómica:

Es el conjunto de ciencias y técnicas dedicadas al estudio integral del funcionamiento, el contenido, la evolución y el origen de la información genética de los diferentes organismos. Esta es una ciencia multidisciplinar que aúna el esfuerzo de biólogos, matemáticos, ingenieros, informáticos, etc...

Epigenética:

Término acuñado por Conrad Hal Waddington en 1953 para referirse al estudio de las interacciones entre genes y ambiente que se producen en los organismos. Tiene mucho que ver con el fenotipo.

Penetrancia genética:

A veces no todos los individuos portadores de una mutación muestran un fenotipo patológico. Cuando la proporción de individuos que muestran el fenotipo patológico es inferior al numero que la portan se dice que el genotipo patológico tiene una penetrancia incompleta.

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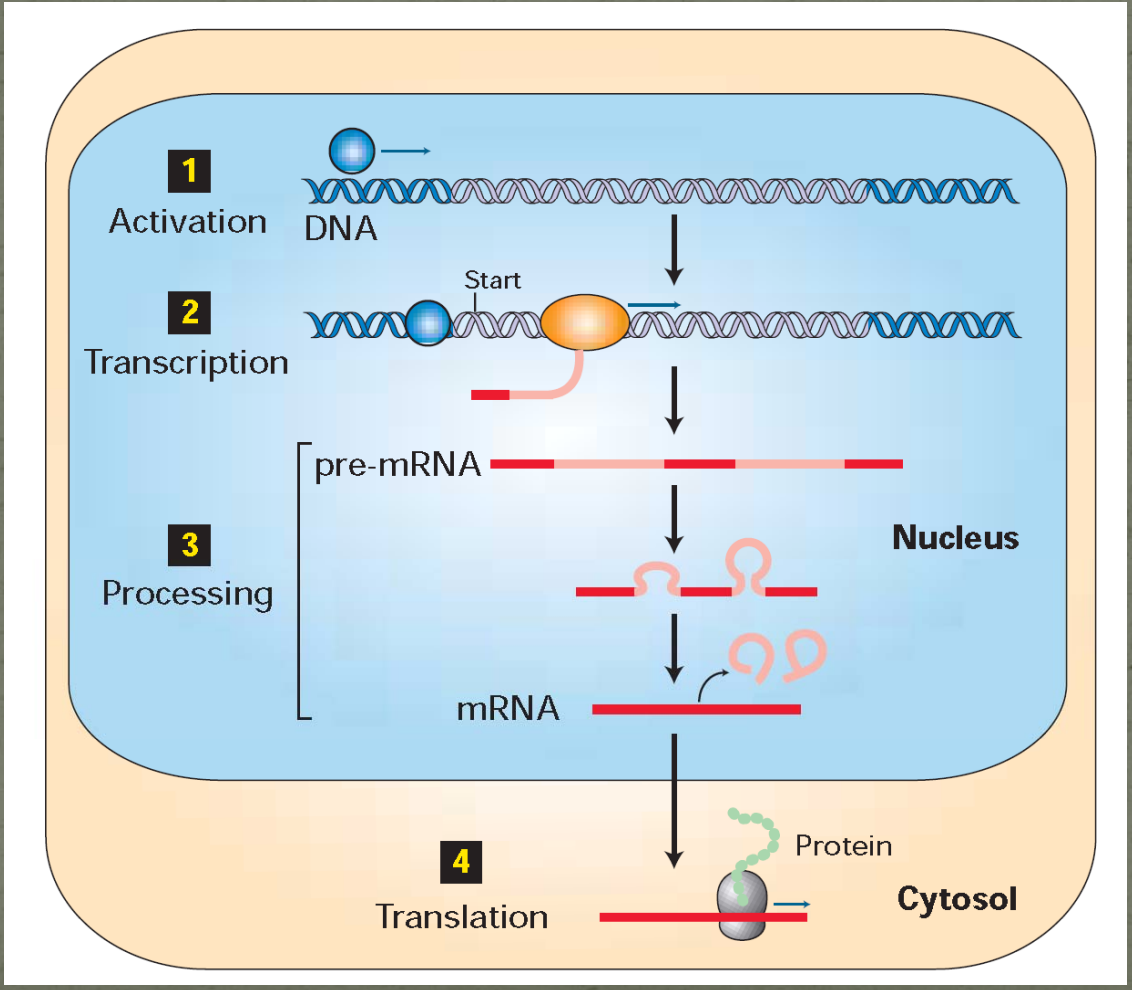
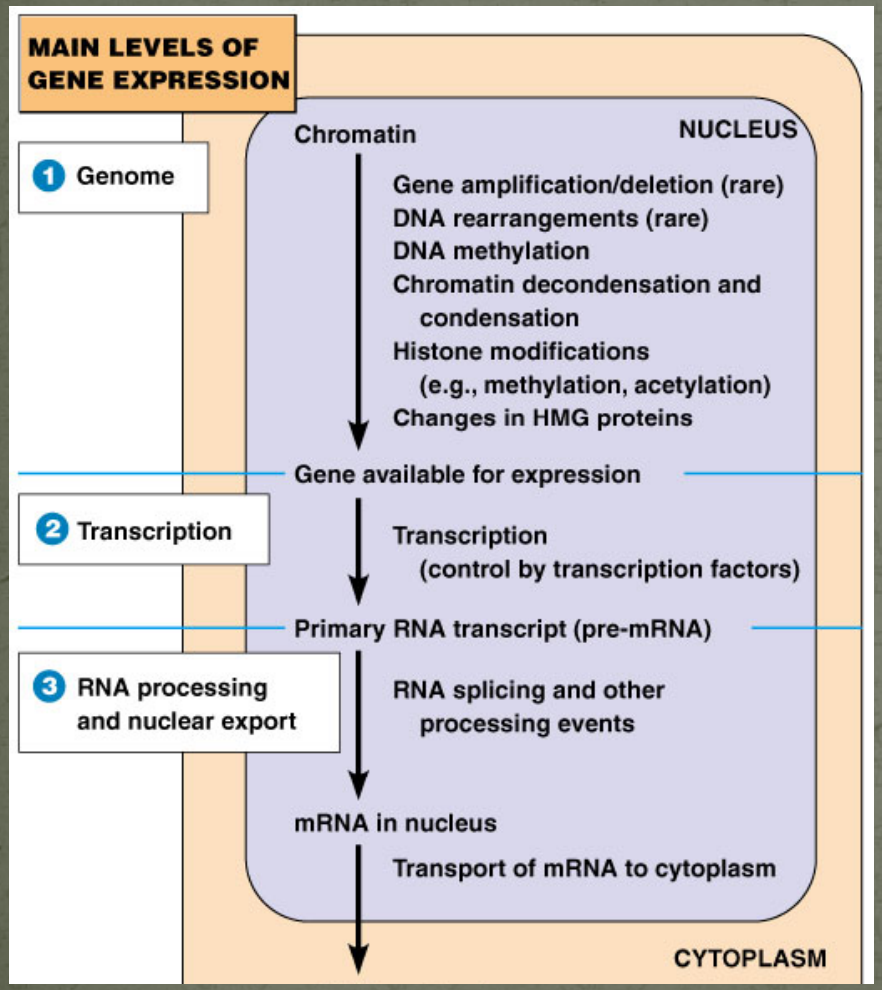
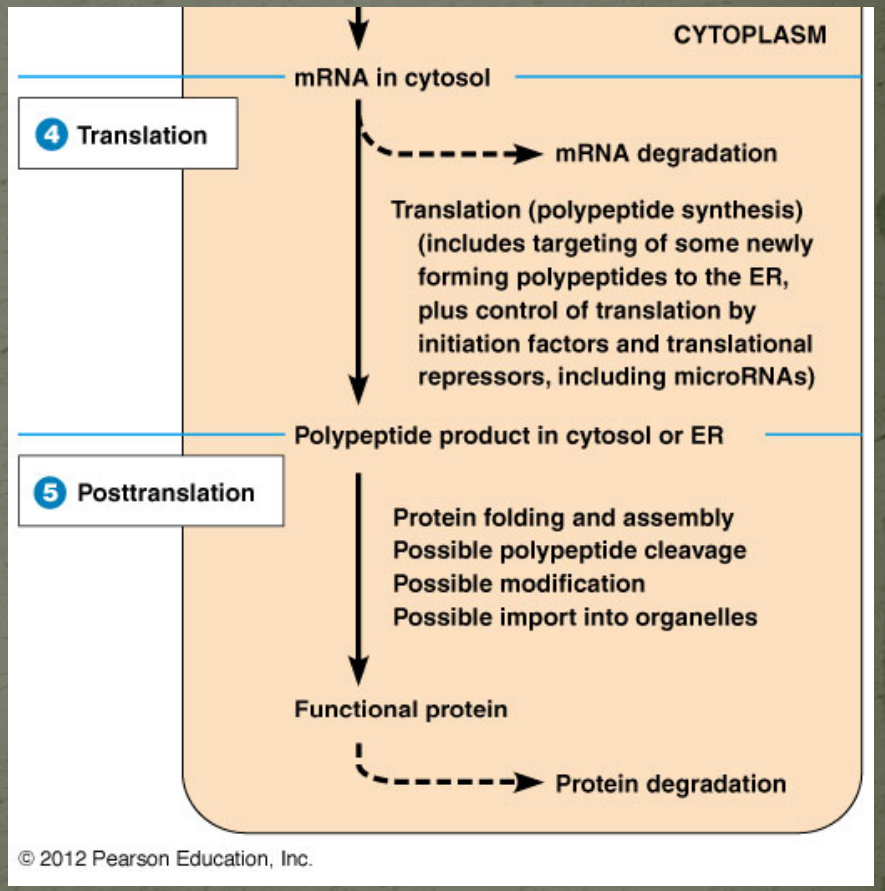


Conceptos básicos de Biología Molecular





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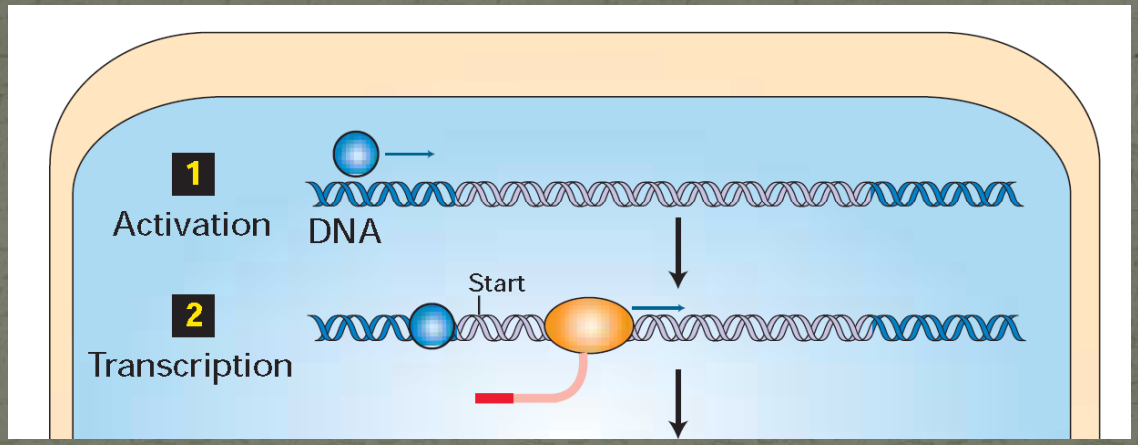
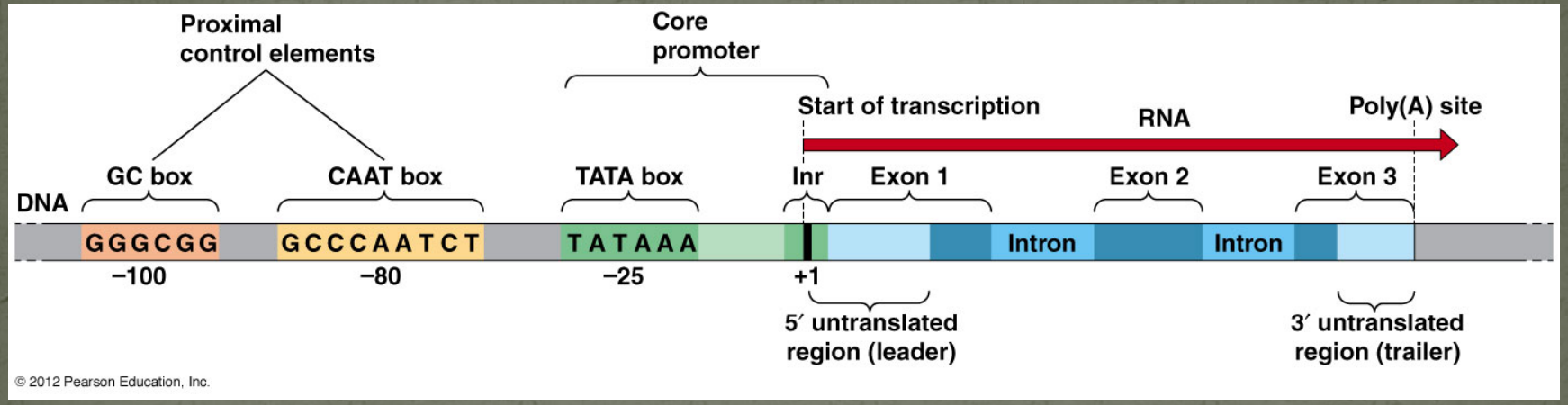


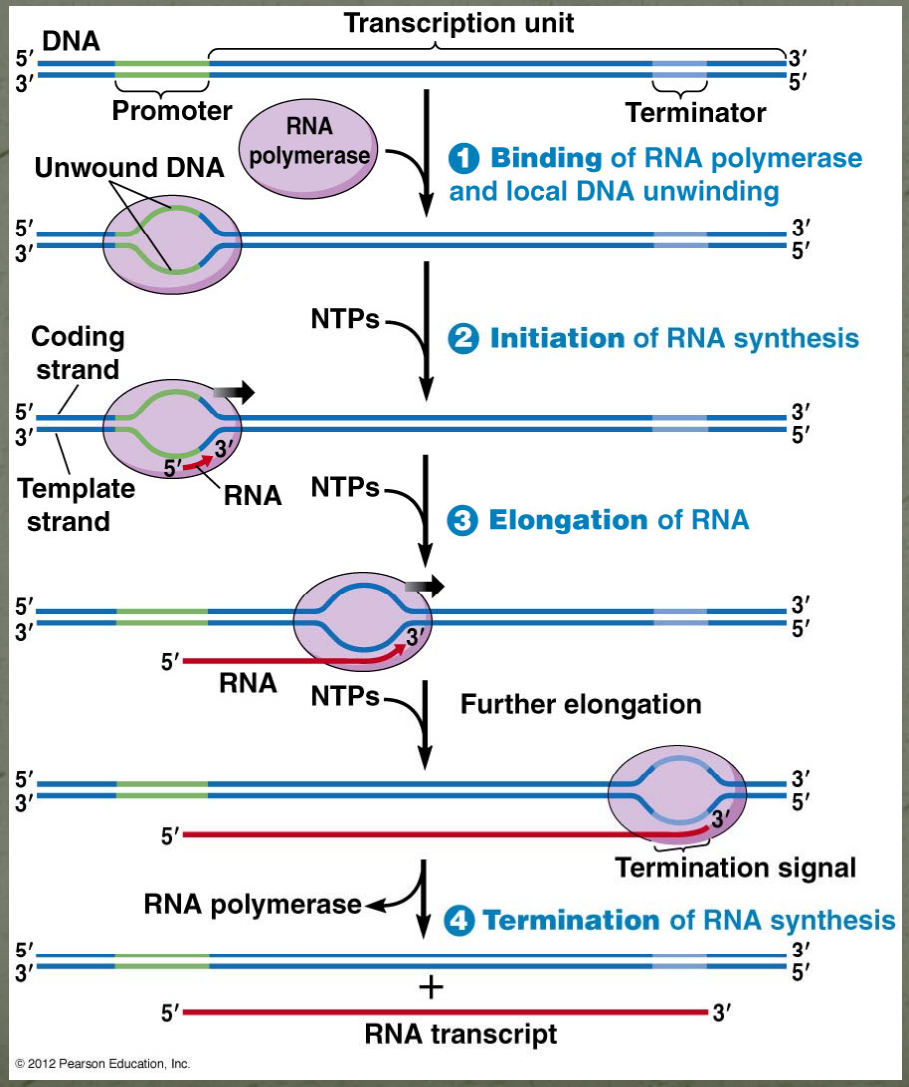
Conceptos básicos de Biología Molecular

Elementos que componen un gen



Los genes son unidades de información que contienen es todos los elementos necesarios para su expresión de manera regulada.

Conceptos básicos de Biología Molecular



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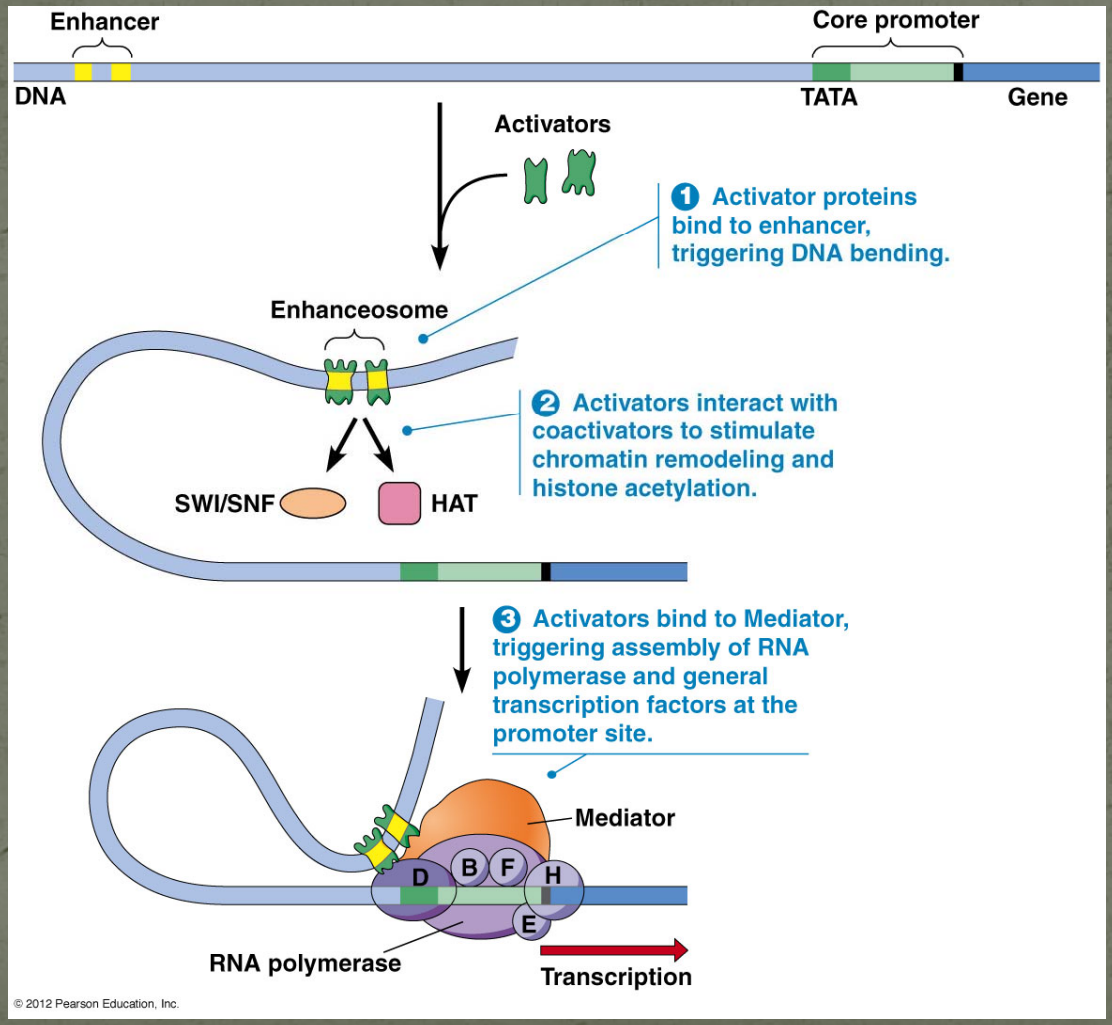

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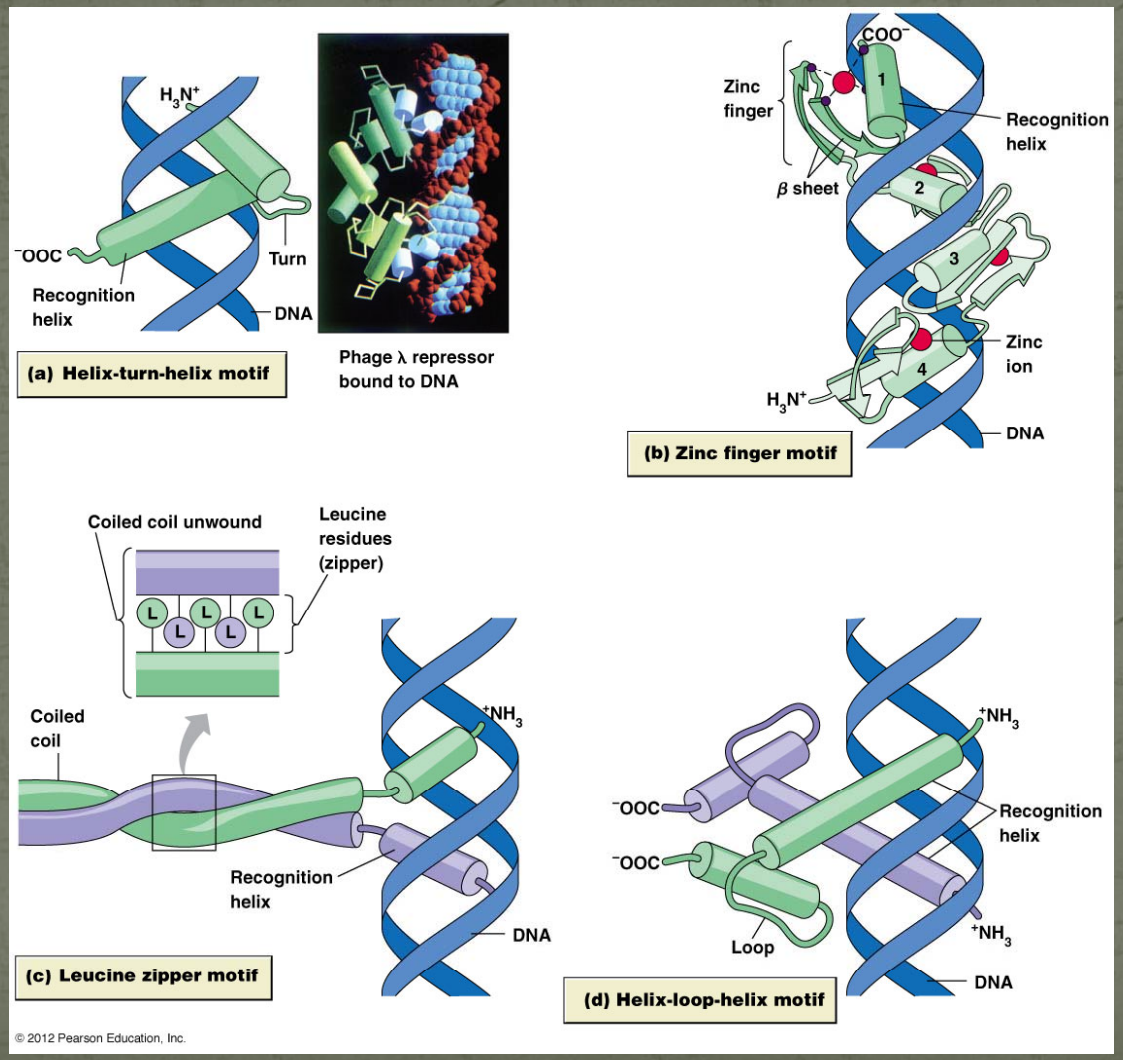

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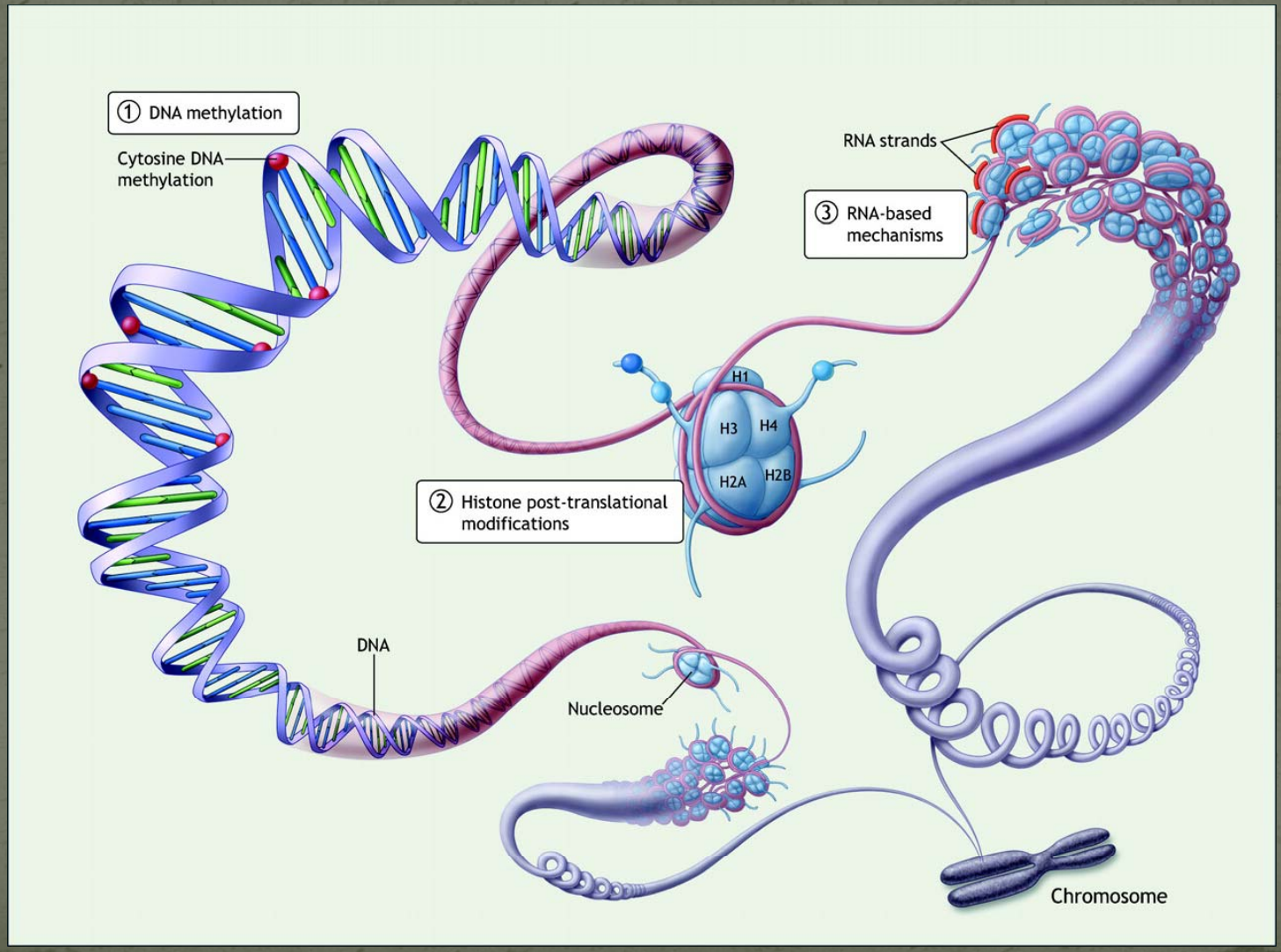

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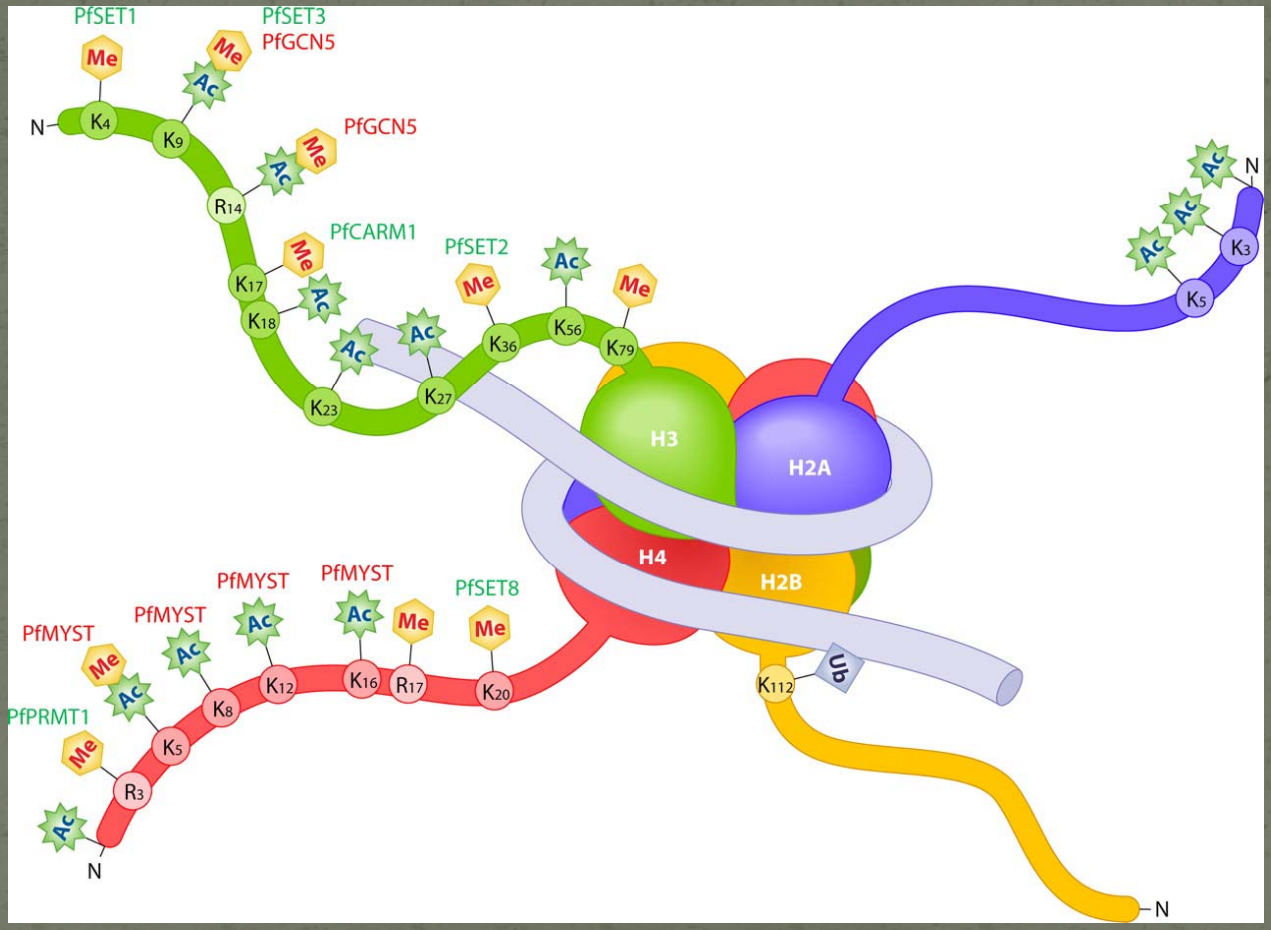

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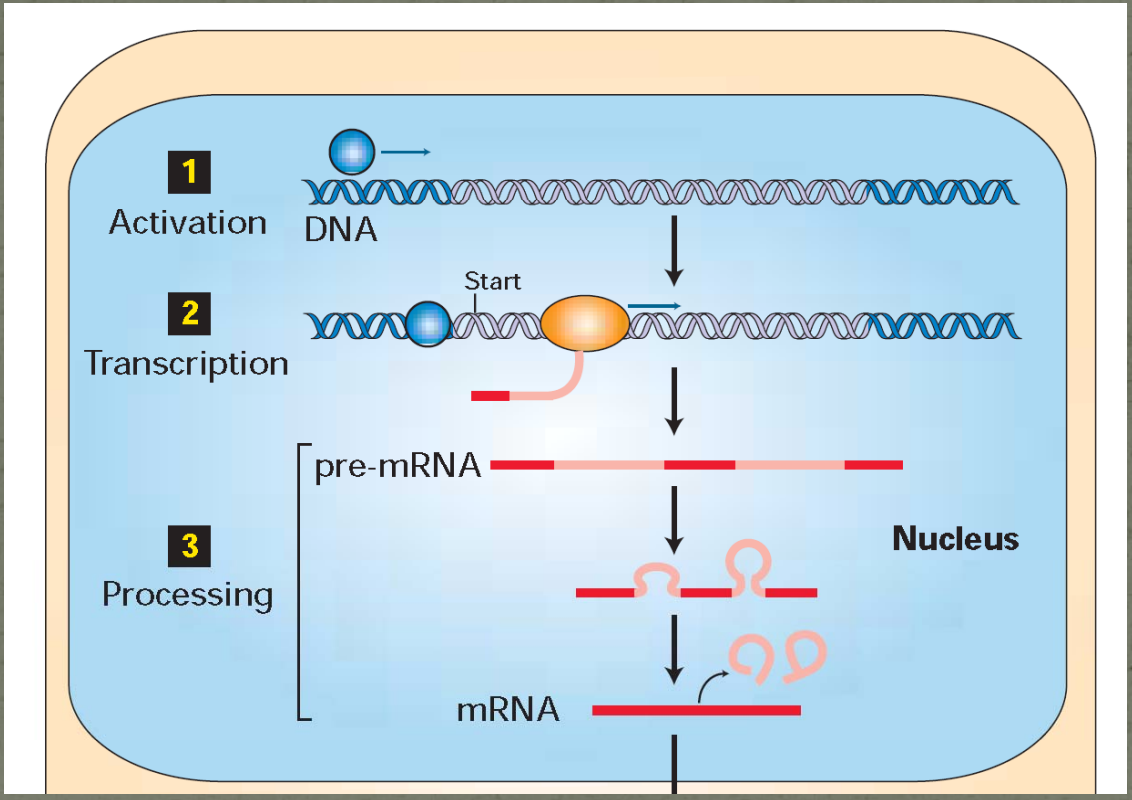

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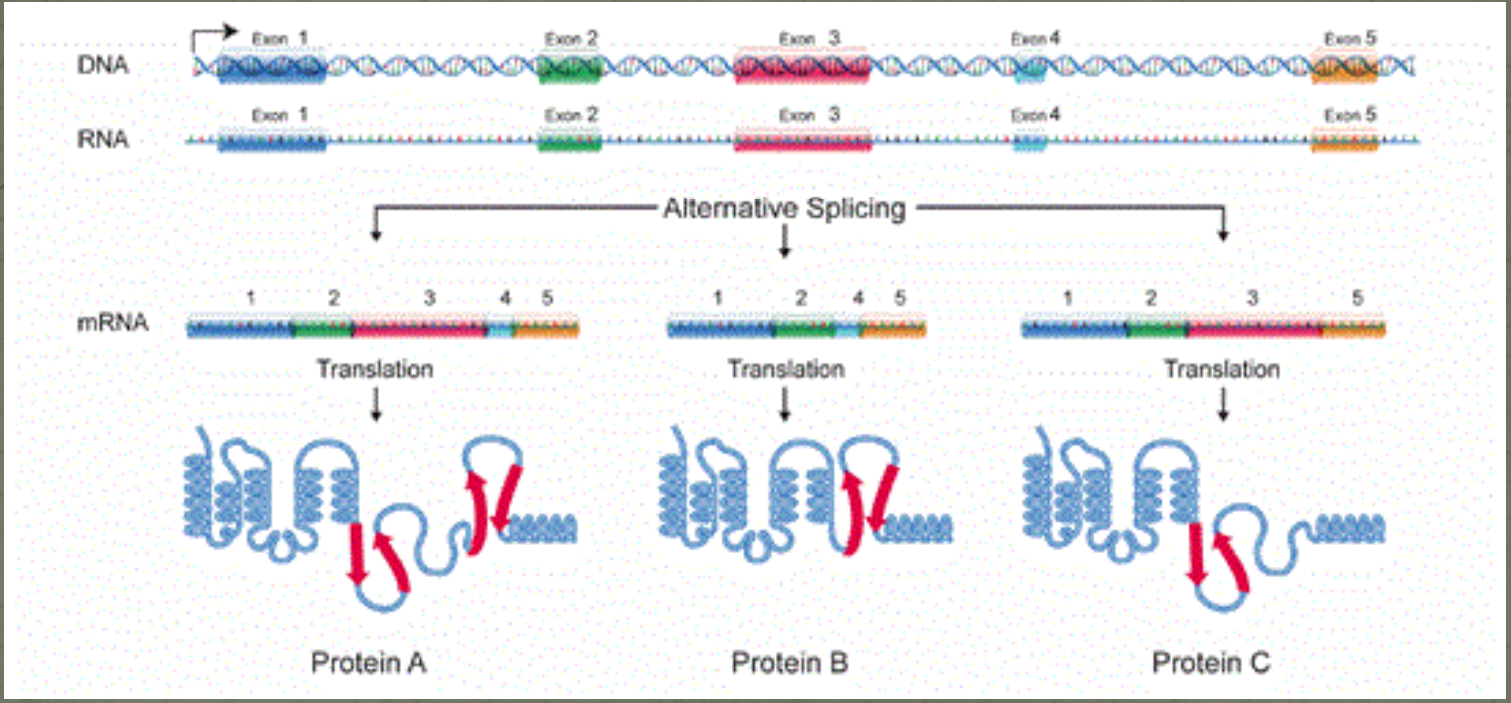
Splicing alternativo



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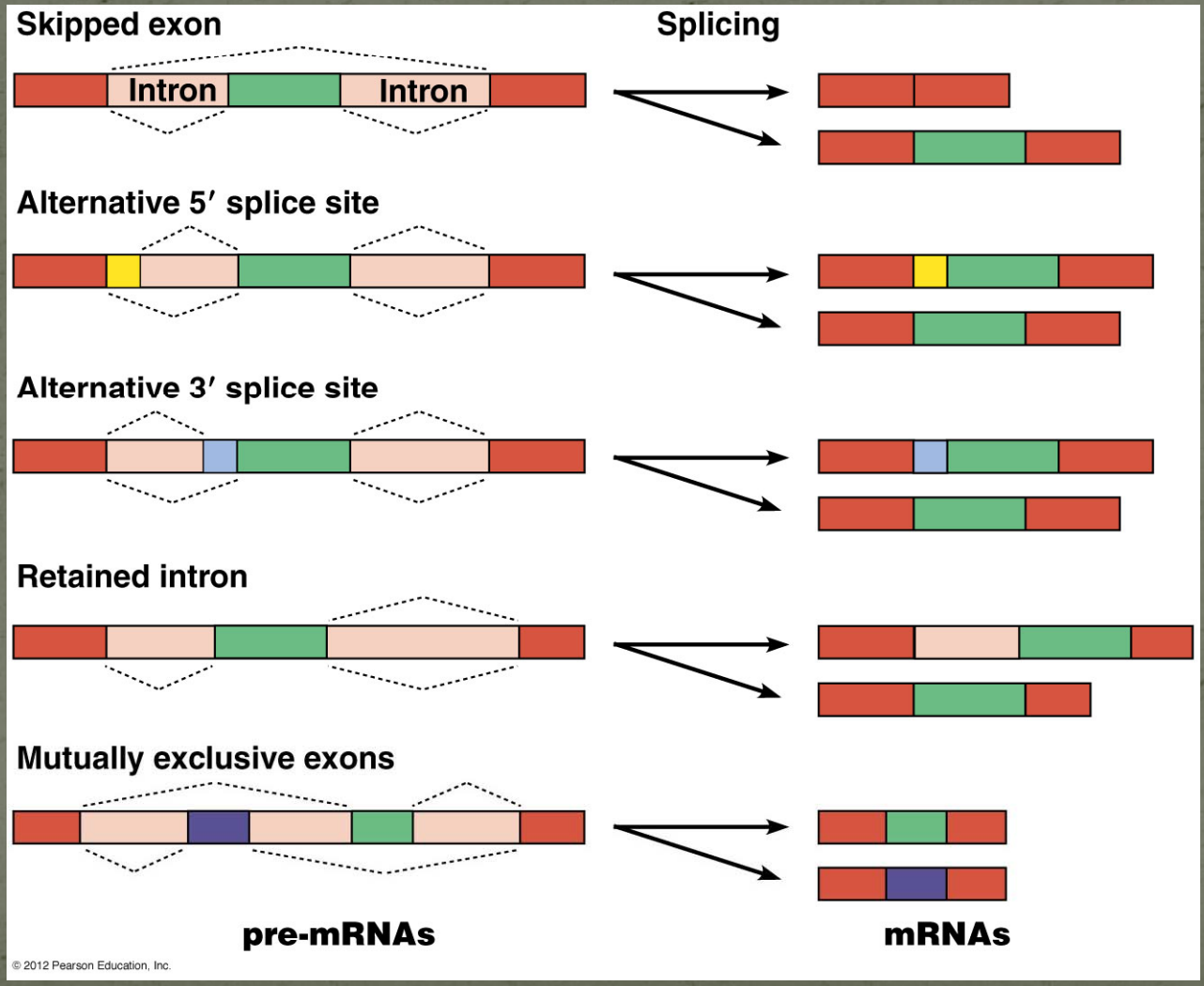

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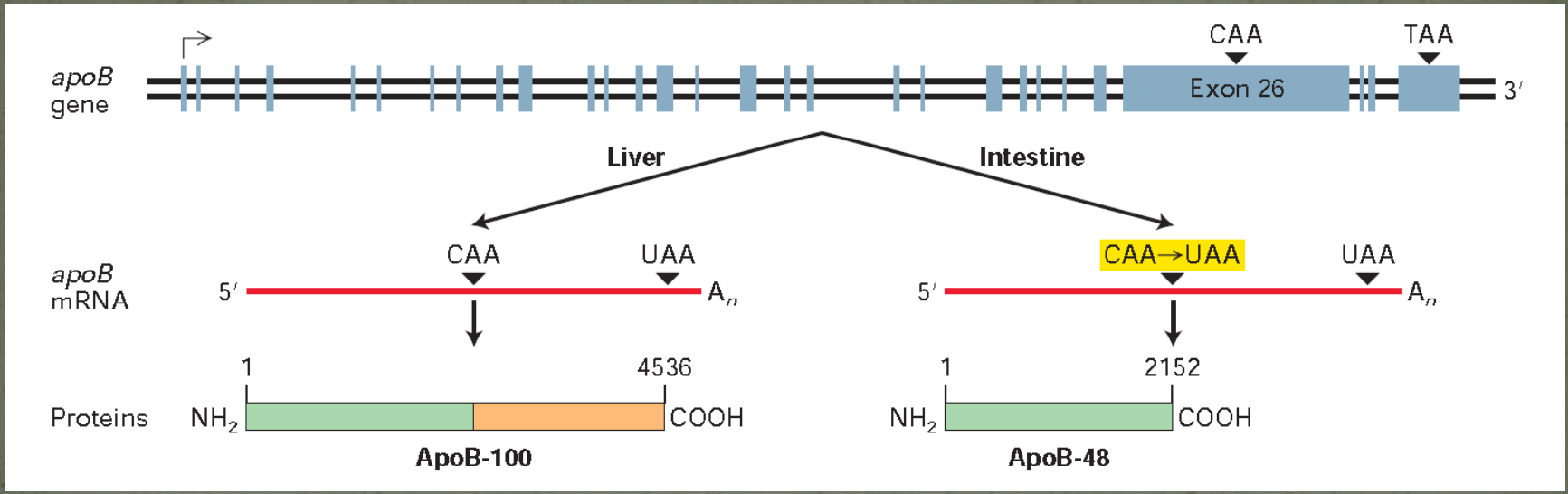
Editado de RNA



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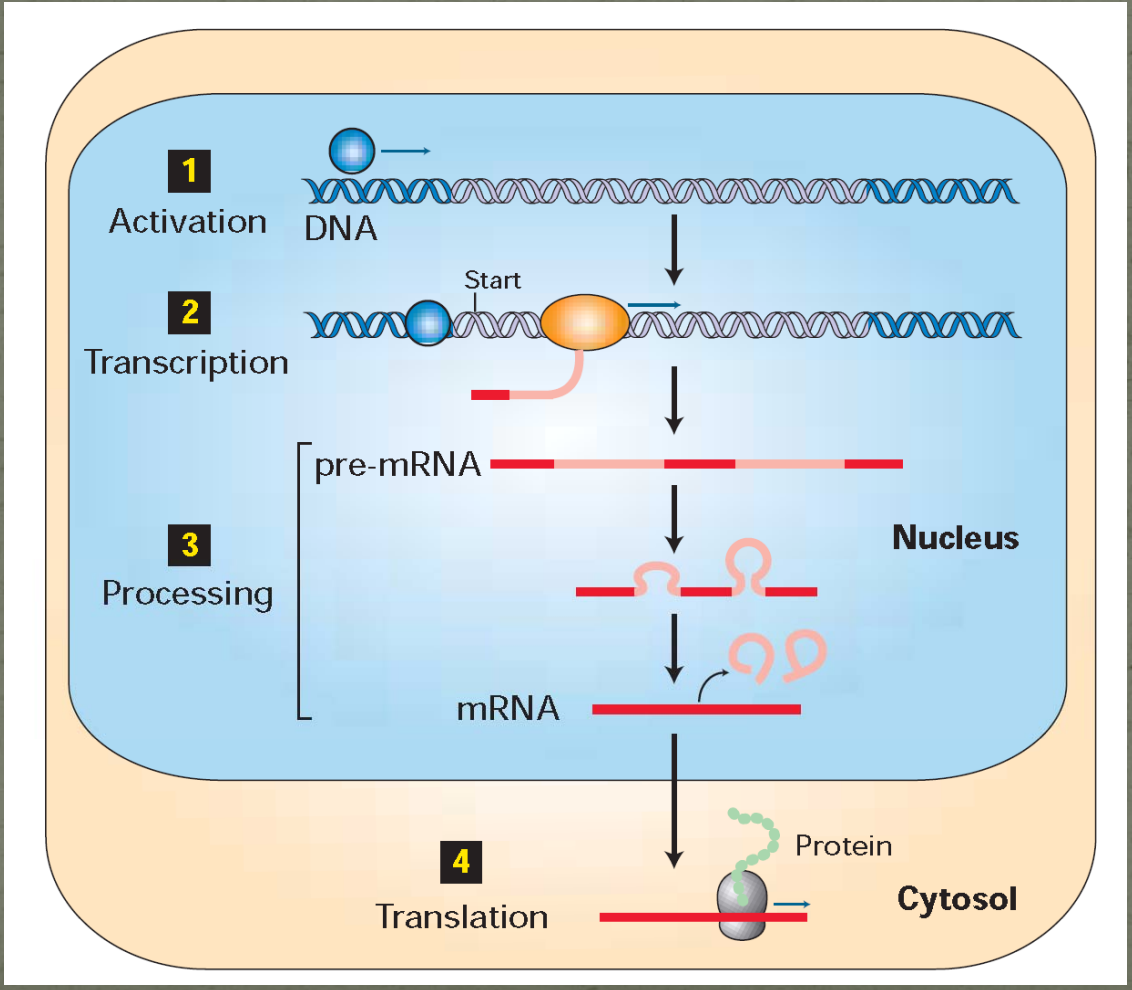

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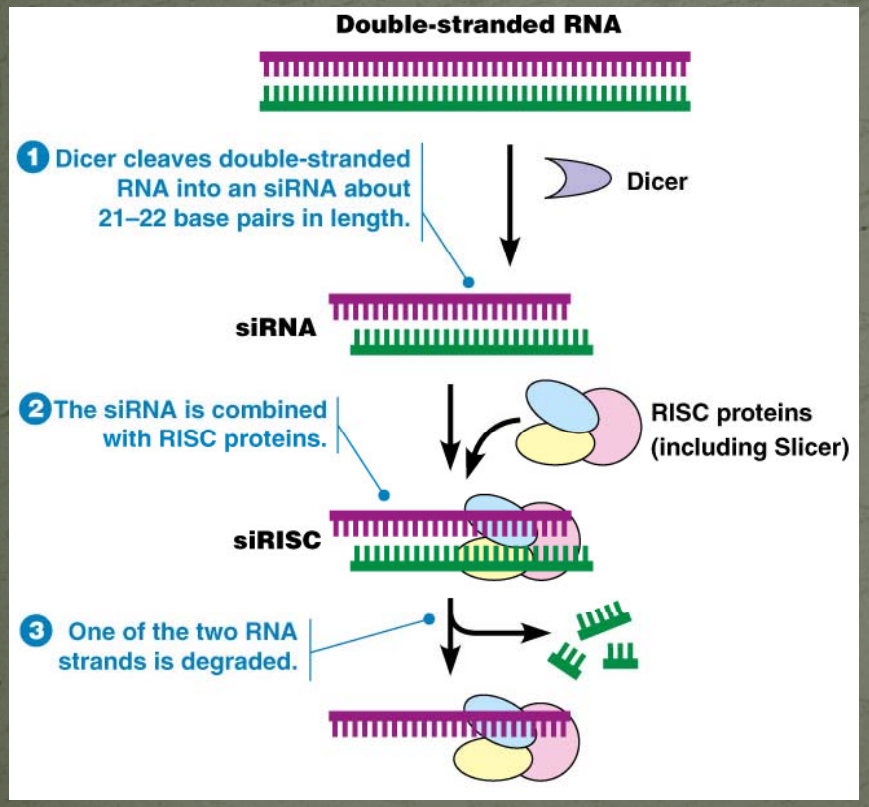

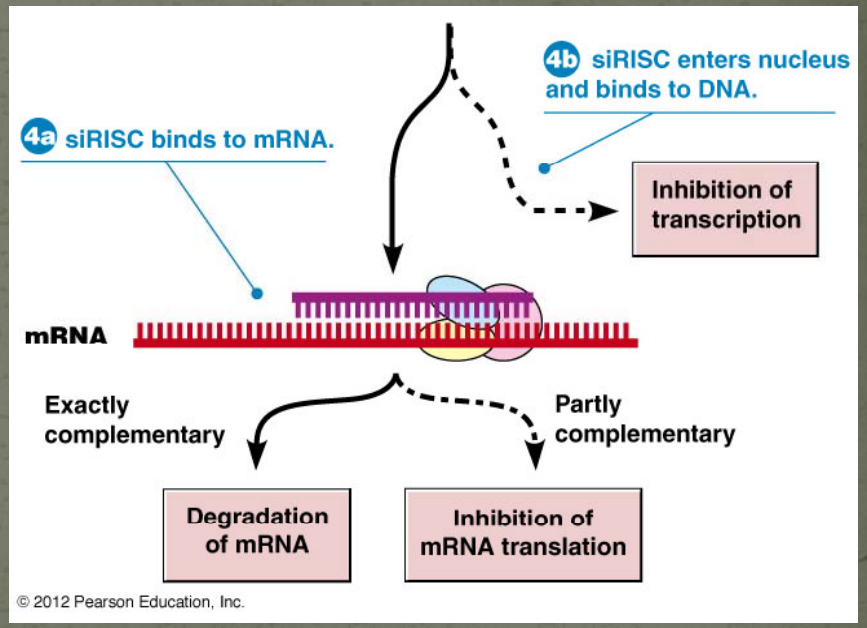

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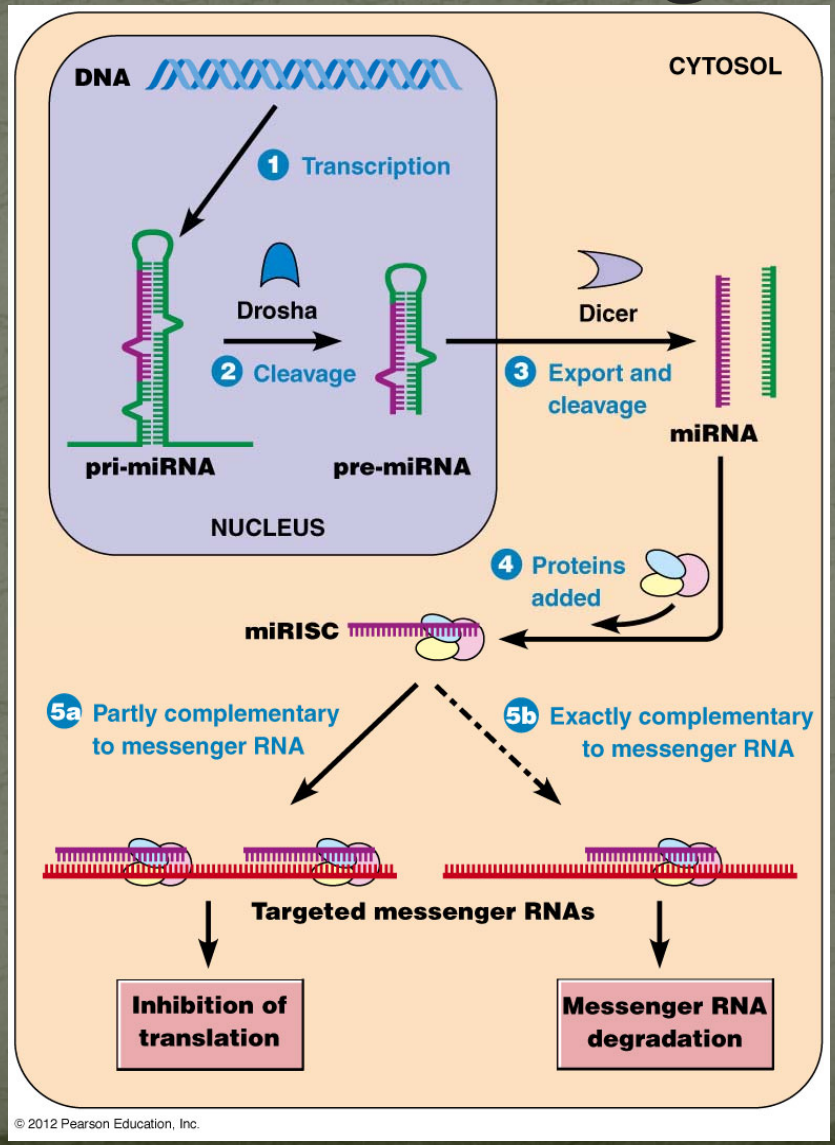
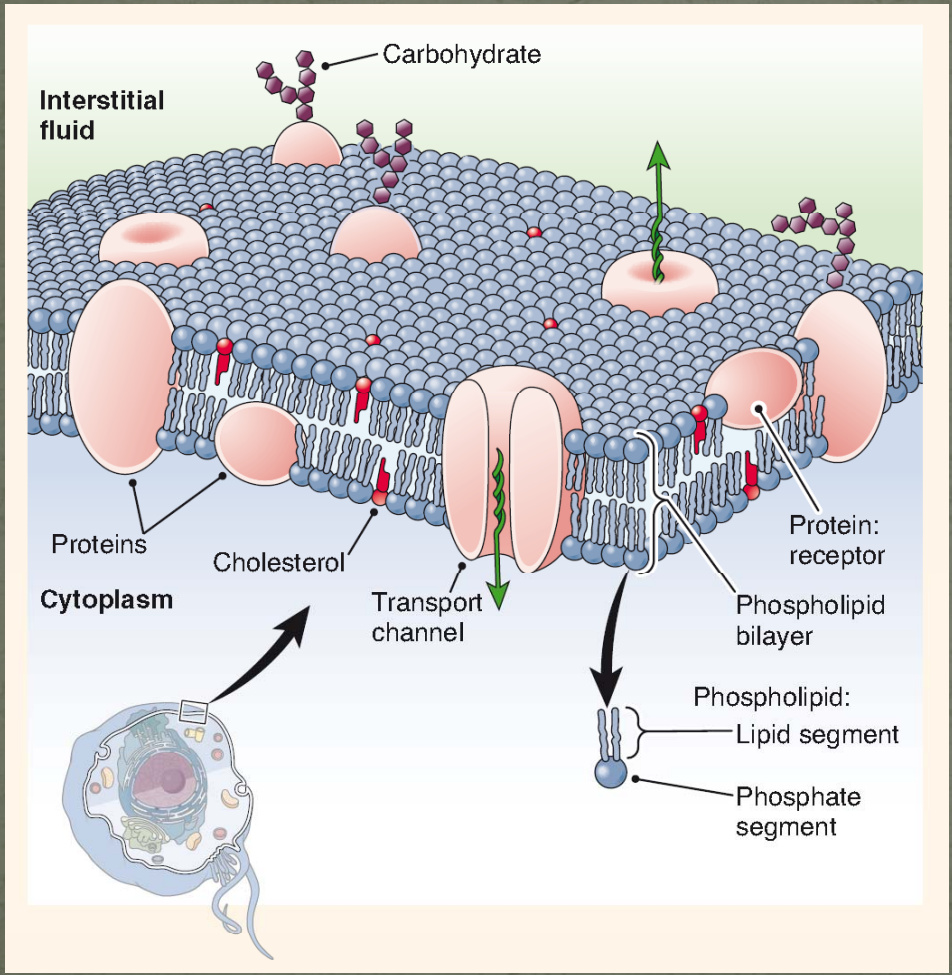


Biología del Colesterol



Síntesis de Esteroides

Precursor de sales Biliares

Precursor de vitamina D

Biología del Colesterol

Sintesis de Colesterol

Citoplasmatica

Requiere NADPH y ATP

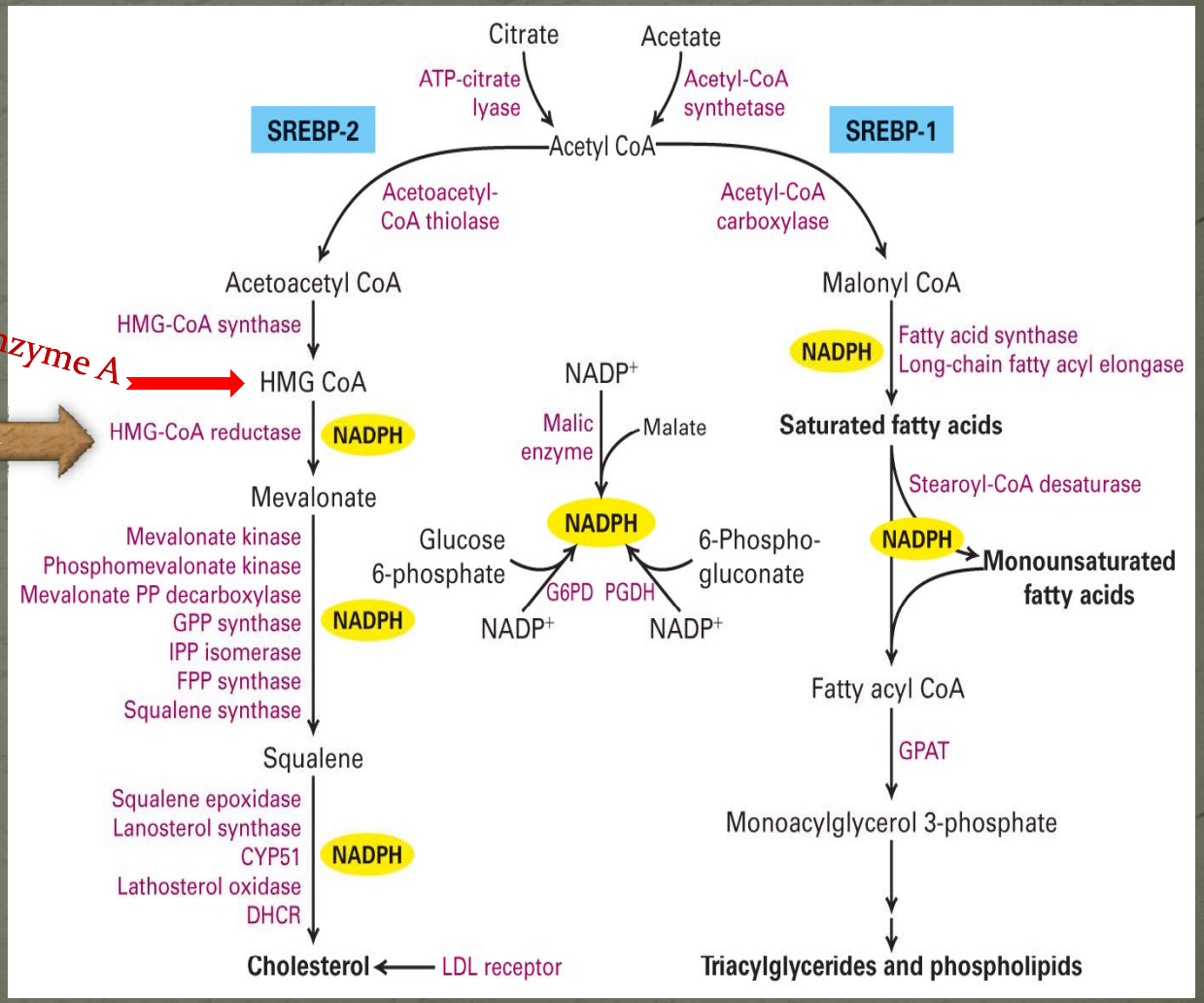
Altamente regulada

80 % en higado, ~10% intestino, ~5% piel

Biología del Colesterol

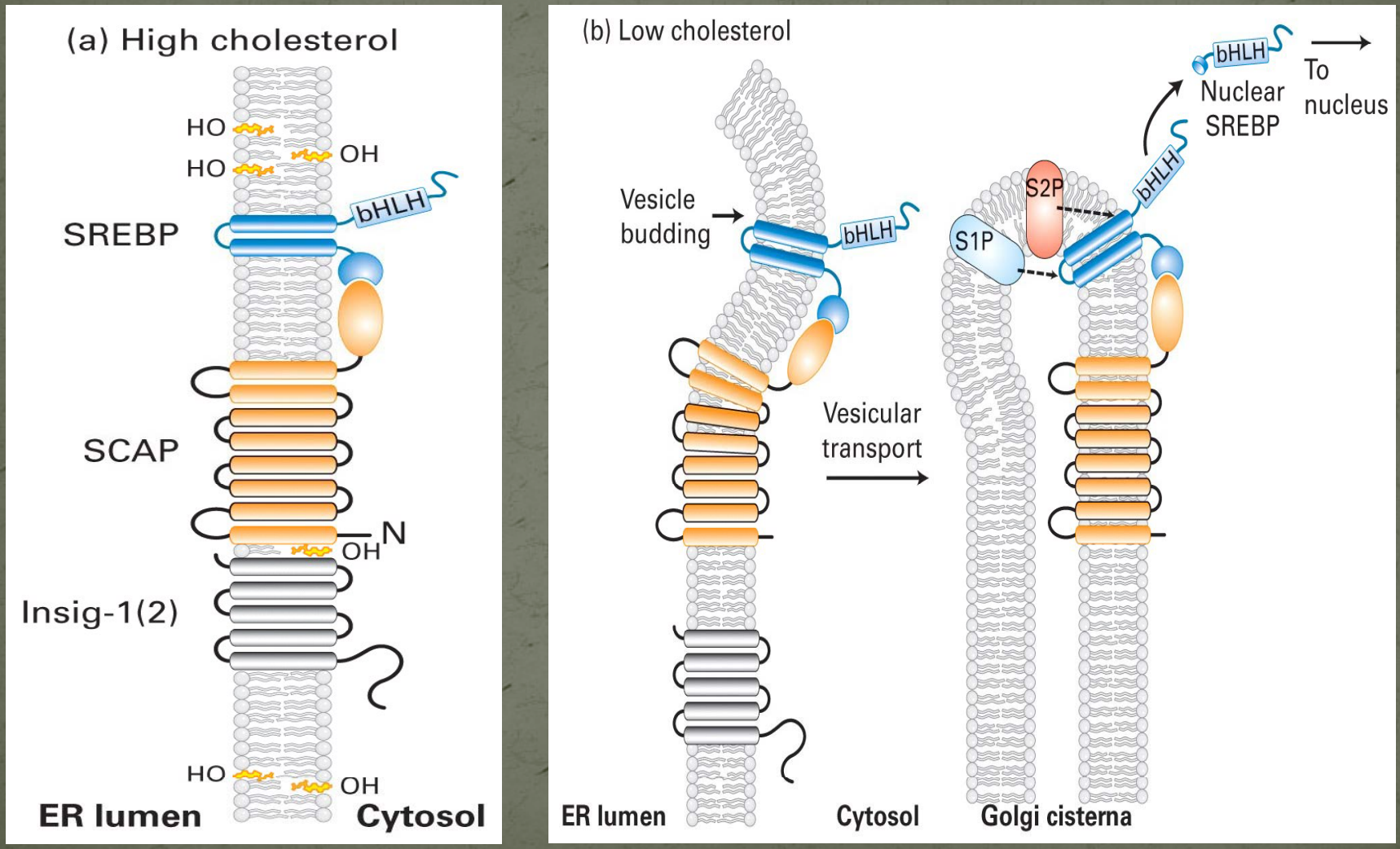
3-hydroxy-3-methylglutaryl-coenzyme A

Estatinas



SREBP: Sterol Regulatory Element-Binding Protein

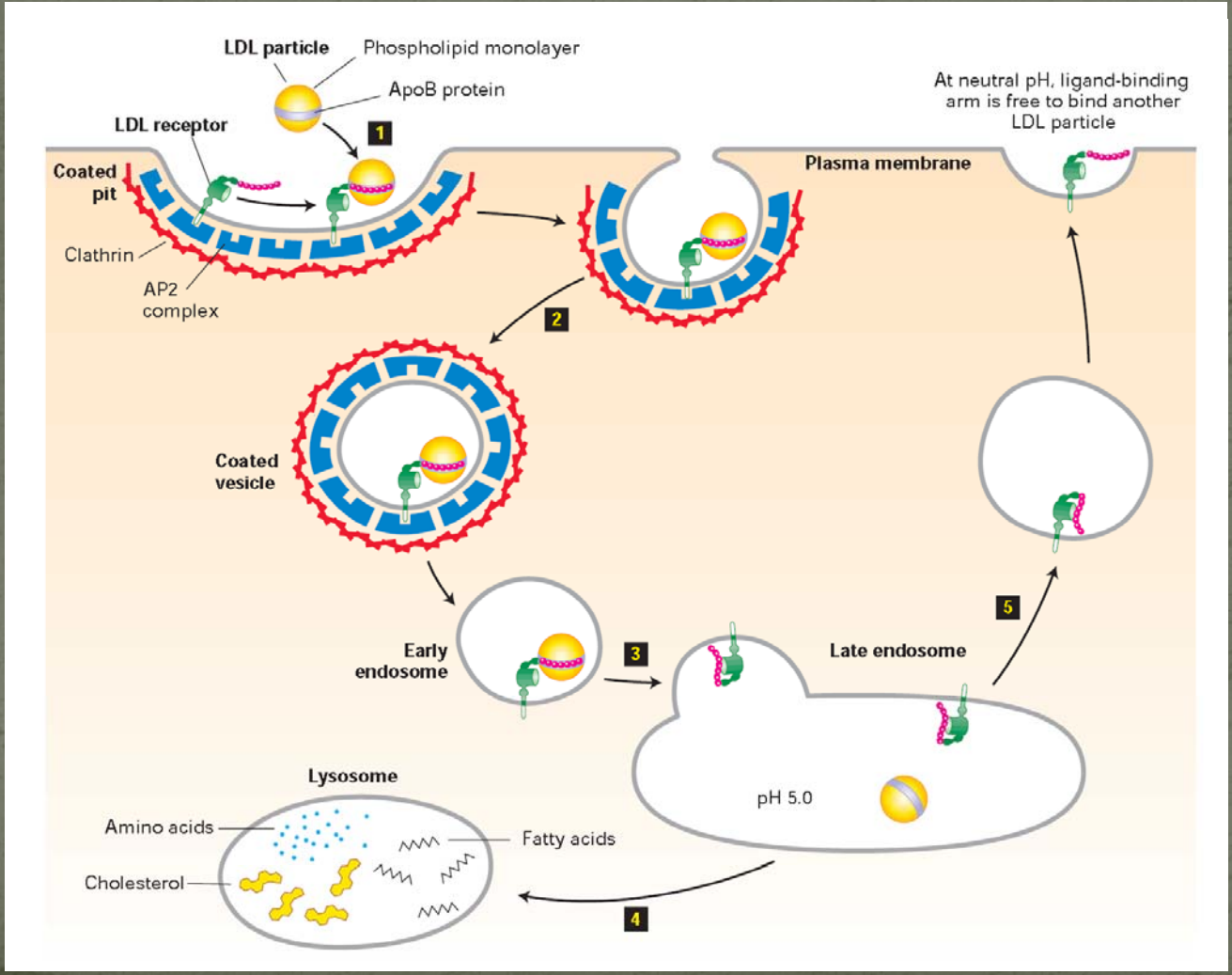
Biología del Colesterol



Biología del Colesterol

Property	Chylomicron	VLDL	LDL	HDL
Mass, approx. (kDa)	50–1000 × 10^3	10–80 ×10^3	2.3 ×10^3	0.175–0.360 ×10^3
Diameter (nm)	75–1200	30–80	18–25	5–12
Triglycerides (% of core lipids)	97	75	12	11
Cholesteryl esters (% of core lipids)	3	25	88	89
Protein:lipid mass ratio	1:100	9:100	25:100	90:100
Major apolipoproteins	A, B-48, C, E	B-100, C, E	B-100	A, C
Major physiological function	Transports dietary triglyceride (Tg) from intestines to extrahepatic tissues (e.g., muscle, adipose tissue); Tg-depleted remnants deliver dietary cholesterol and some Tg to the liver	Transports hepatic Tg to extrahepatic tissues; converted into LDL	Transports plasma cholesterol to liver and to extrahepatic tissues	Takes up cholesterol from extrahepatic tissues and delivers it to liver, steroid-producing tissues, and other lipoproteins

Biología del Colesterol



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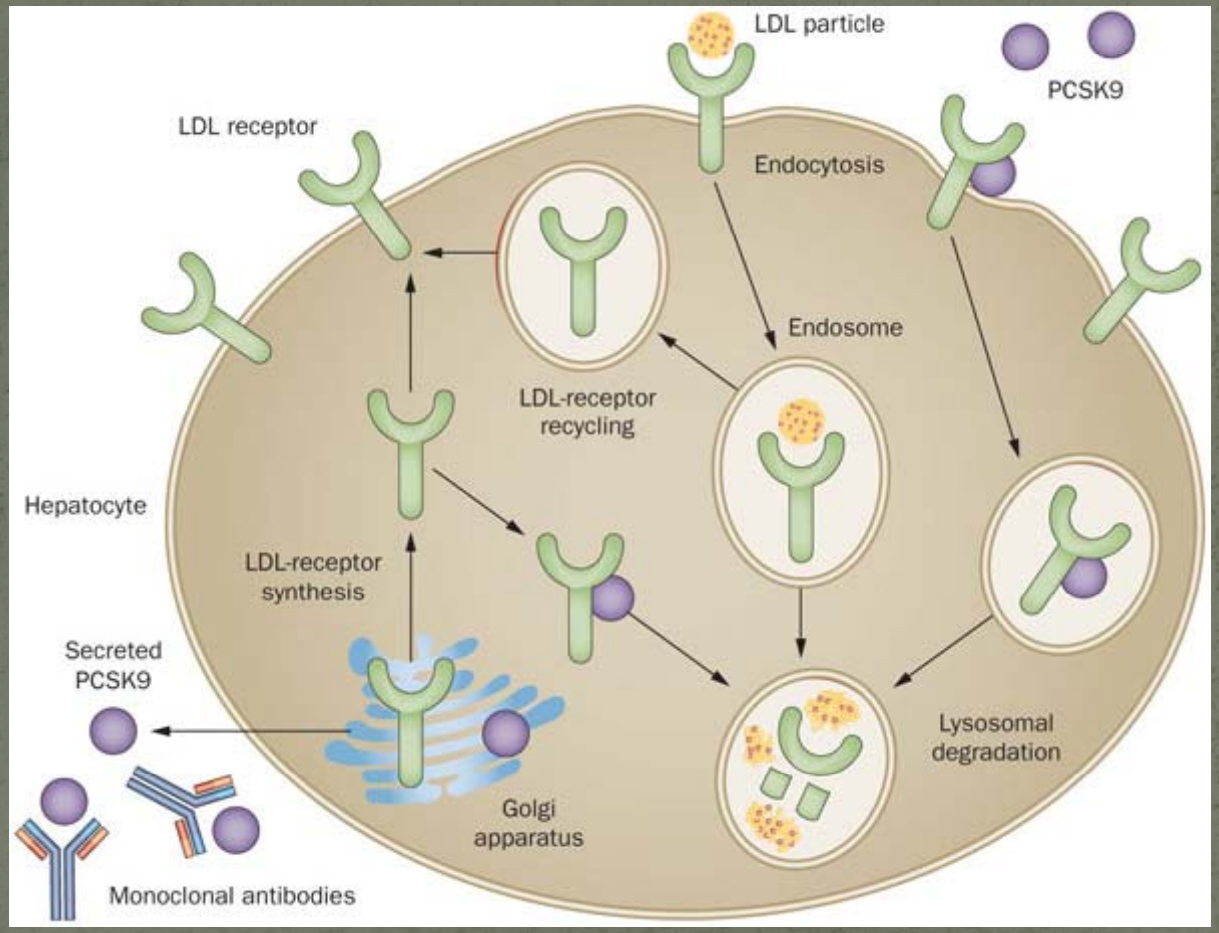


Genética y Genómica

Hipercolesterolemia Familiar

Enfermedad genética monogénica.
Genes implicados:

LDLR (prevalencia 1 en 500, varía entre poblaciones)
ApoB (prevalence 1 en 1000)
PCSK9 (prevalencia menos de 1 in 2500)
LDLRAP1.

Genética y Genómica

Hipercolesterolemia Familiar

LDLR

Se han documentado mas de 1000 variantes entre SNPs y mutaciones.

Clase I: no se sintetiza (NMD)
Clase II: No se transporta del ER al Golgi
Clase III: No une LDL
Classe IV: no interacciona con Clatrina
Clase V: no se recicla a la superficie

Los interesados consultar la base de datos: **Online Mendelian Inheritance in Man (OMIM)**. En esta base de datos se catalogan continuamente enfermedades que se asocian con genes

Genética y Genómica

Como descubrir nuevos genes relacionados con Hipercolesterolemia

Una de las aproximaciones mas modernas es el **estudio de asociación del genoma completo** (en inglés, GWAS (Genome-wide association study), que es un análisis de una variación genética a lo largo de todo el genoma humano con el objetivo de identificar su asociación a un rasgo observable. Los GWAS suelen centrarse en asociaciones entre los polimorfismos de un solo nucleótido (SNPs) y rasgos como las principales enfermedades.

Cuando se combina GWAS con Metabolomica este análisis se sofistica y puede dar resultados espectaculares.

HUMAN LONGEVITY, INC.

Genética y Genómica

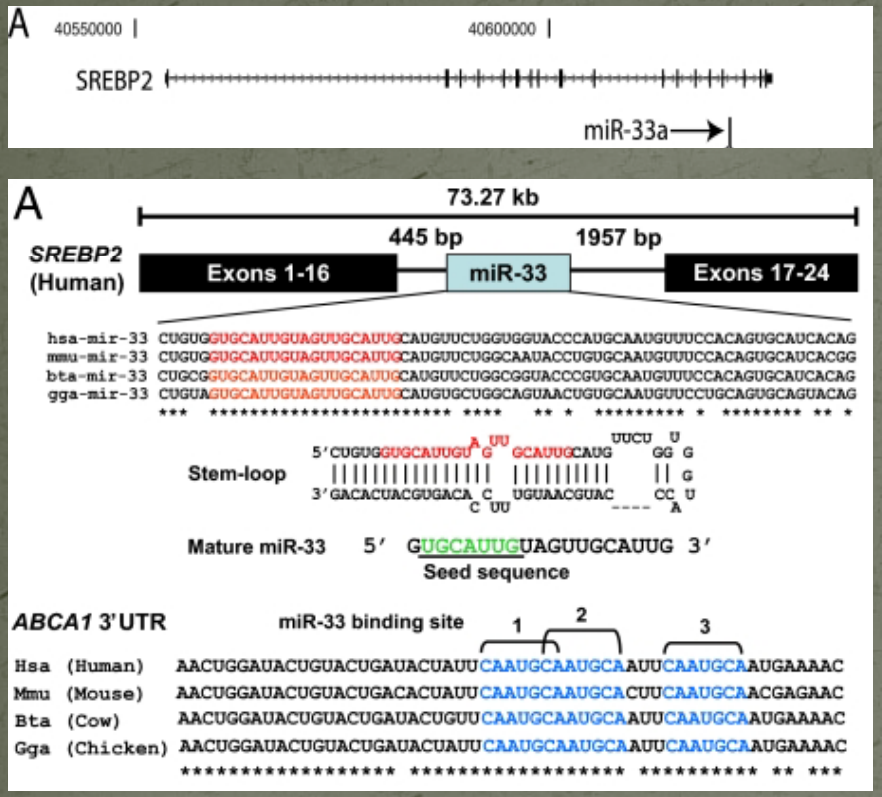
¡¡¡¡¡¡¡Advertencia!!!!!!!!

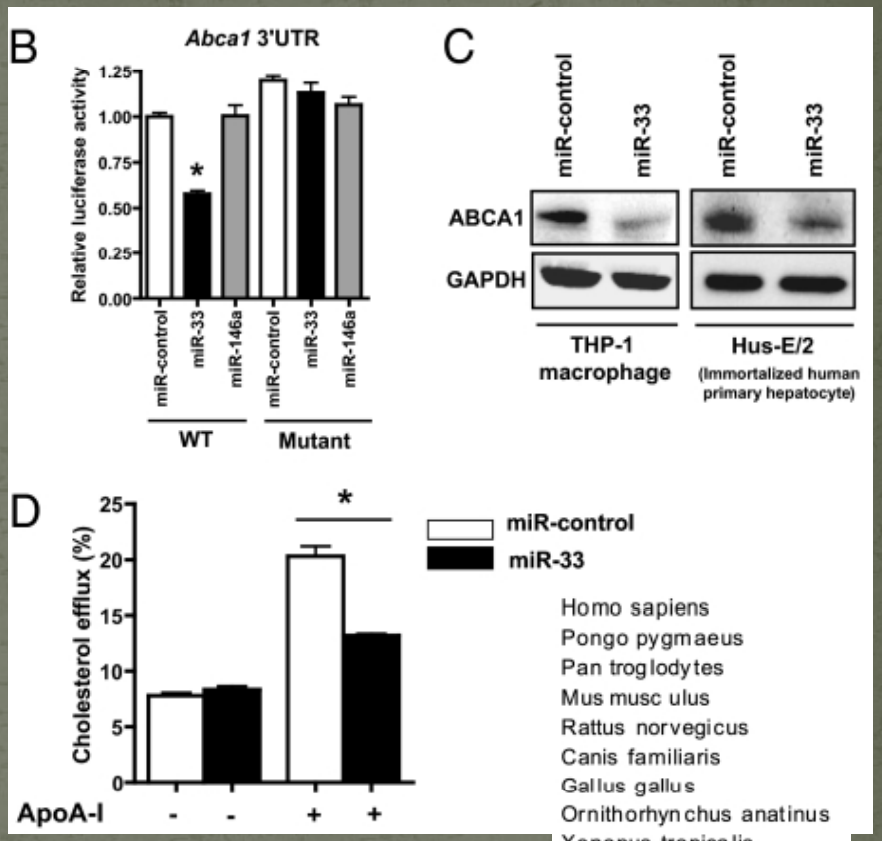
La genómica no es la panacea.

El Splicing Alternativo es una manifestación fenotípica.

El Splicing Alternativo posiblemente media la conexión entre la nutrición, hábitos de vida y hipercolesterolemia.

Nuevas terapias de base genética



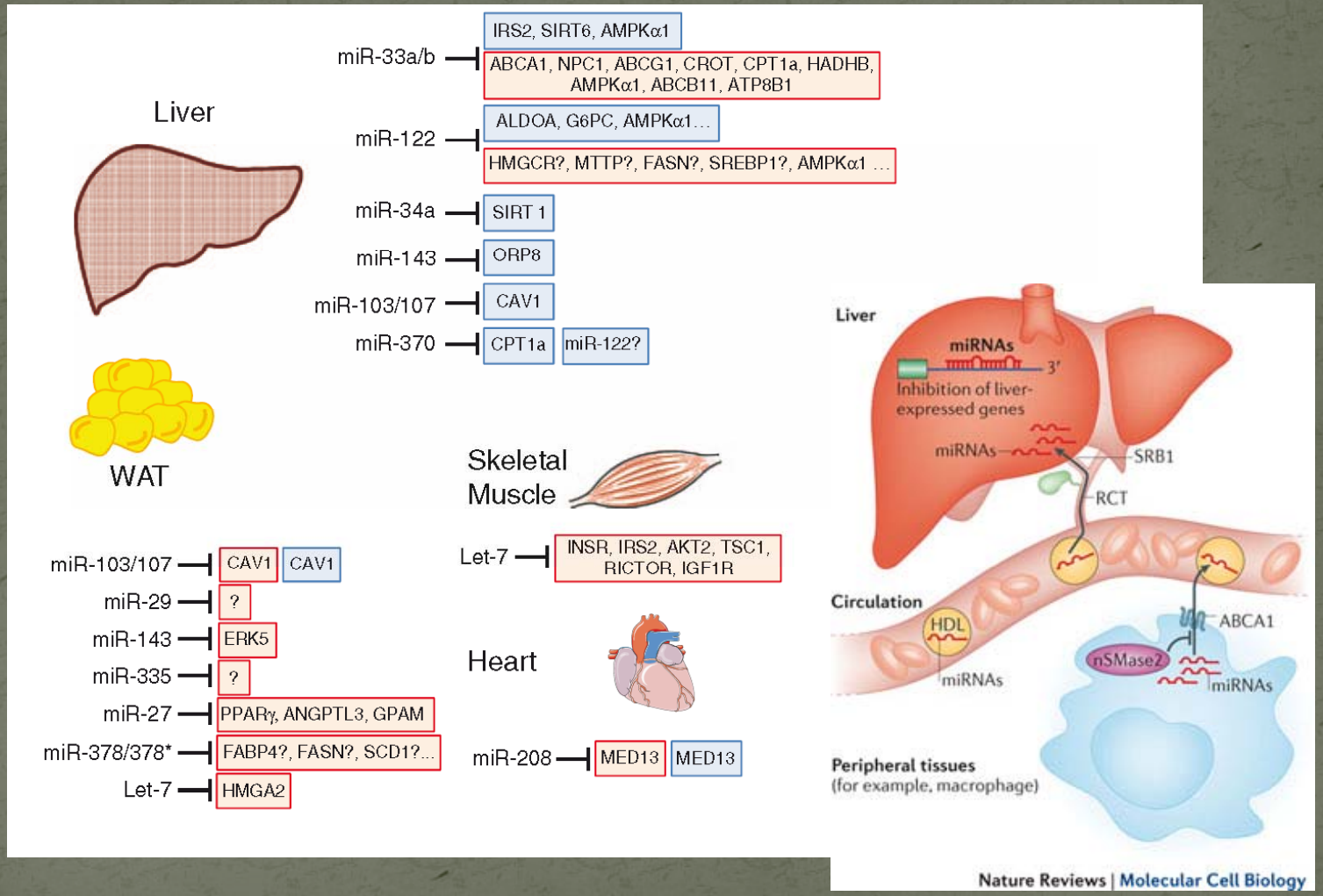


Homo sapiens
Pongo pygmaeus
Pan troglodytes
Mus musculus
Rattus norvegicus
Canis familiaris
Gallus gallus
Ornithorhynchus anatinus
Xenopus tropicalis
Ciona intestinalis
Tribolium castaneum
Apis mellifera
Drosophila melanogaster

ABCA1, an ATP-binding cassette transporter which promotes cellular phospholipid and cholesterol efflux

Proc Natl Acad Sci U S A. 2010; 107(40): 17321–17326.

Nuevas terapias de base genética



Metabolismo lipídico

Metabolismo glucosa

Biología del Colesterol

Table 1: MicroRNAs involved in cholesterol metabolism.

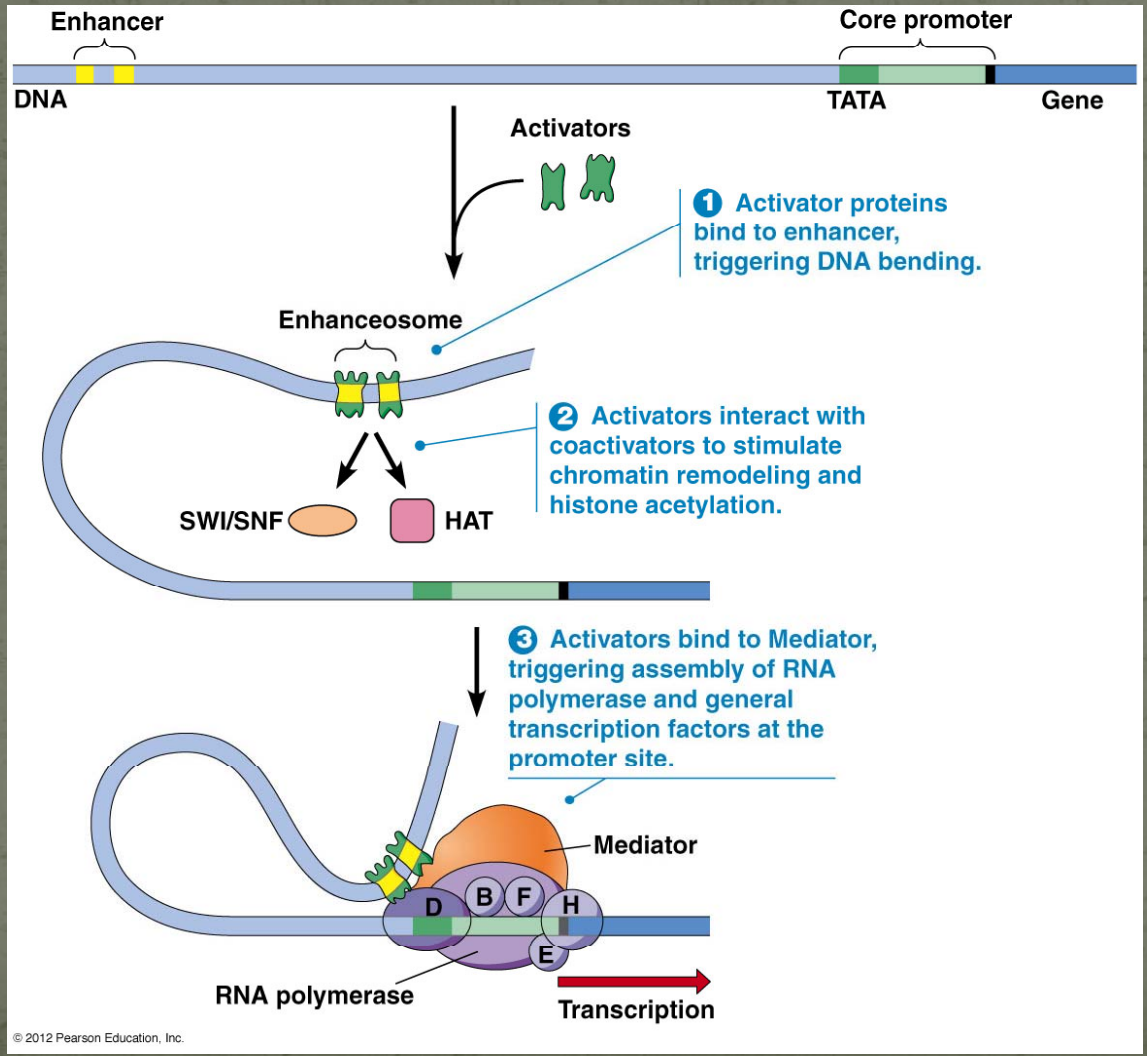
miRNA	Target tissue/cell type	Target genes	Biological function
miR-122	Primary mouse hepatocytes	*ALDOA* *CS*	Glucose homeostasis Krebs cycle
miR-33a and miR-33b	Liver and macrophage	*ABCA1; ABCG1; NPC1* *CROT; HADHB; CPT1; SIRT6; PRKAA1* *IRS2*	Cellular cholesterol efflux Fatty acid oxidation Insulin signaling
miR-758	Human and mouse macrophages and hepatic cell line	*ABCA1*	Cellular cholesterol efflux
	Human neuroglioma cell line	*SLC38a1; NTM; EPHA7*	Aminoacid synthesis, neurite outgrowing, and neuronal migration
miR-106b	Mouse neuroblastoma cell line and human hepatocyte	*ABCA1*	Cellular cholesterol efflux and Aβ production

Hindawi Publishing Corporation
Cholesterol
Volume 2012, Article ID 847849, 8 pages
doi:10.1155/2012/847849

Review Article

MicroRNA Regulation of Cholesterol Metabolism

Noemi Rotllan and Carlos Fernández-Hernando


Enhancer
Core promoter
DNA
TATA
Gene
Activators
1 Activator proteins bind to enhancer, triggering DNA bending.
Enhanceosome
2 Activators interact with coactivators to stimulate chromatin remodeling and histone acetylation.
SWI/SNF
HAT
3 Activators bind to Mediator, triggering assembly of RNA polymerase and general transcription factors at the promoter site.
Mediator
D
B
F
H
E
RNA polymerase
Transcription
© 2012 Pearson Education, Inc.

Nuevas terapias de base genética

Uso de miRNA

Although the roles of the sterol response element binding protein-1 (SREBP1) and SREBP2 transcription factors in regulating fatty acid and cholesterol synthesis and uptake have been known for some time, it was recently discovered that 2 related microRNAs (miRs), *miR-33a* and *miR-33b*, are embedded in these genes. Studies indicate that *miR-33a* and *miR-33b* act with their host genes, *Srebp2* and *Srebp1*, respectively, to reciprocally regulate cholesterol homeostasis and fatty acid metabolism in a negative feedback loop. miR-33 has been shown to posttranscriptionally repress key genes involved in cellular cholesterol

Conceptos básicos de Biología Molecular

Cardiovascular disease is highly prevalent throughout the world and is the leading cause of morbidity and mortality in the USA. Atherosclerosis results from the interaction of environmental and genetic risk factors, including age, sedentary life style, cigarette smoking, dyslipidemia, hypertension, obesity, and diabetes mellitus. About 50% of susceptibility to cardiovascular disease is genetic including polymorphisms affecting risk factors . Despite widely prescribed drugs such as statins to lower cholesterol levels, there is wide range of variability in drug response in terms of both lipoprotein and cardiovascular risk reduction. Identifying genes responsible for coronary atherosclerosis and biomarkers for quantifying an individual risk of cardiovascular disease will enable personalized medicine based on the individual's genetic variants.

Several cis-acting SNPs that regulate alternative splicing of HMGCR and LDLR have been identified by genome-wide association analysis (GWAS) to contribute to inter-individual variation in plasma LDL-cholesterol in multiple independent populations . Among them, a common polymorphism (rs688) within low density lipoprotein receptor (LDLR) has been shown to be associated with increased plasma LDL-cholesterol via promoting LDLR exon 12 skipping . In addition, several of the mutations within LDLR associated with FH disrupt normal LDLR pre-mRNA splicing result in reduced LDLR cell surface protein and LDL internalization . A 10-candidate-gene association study of the prospectively executed Pravastatin Inflammation/CRP Evaluation (PRINCE) study have found that two highly linked SNPs (rs17244841 and rs17238540) in the 3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) gene (the direct target of statin inhibition) were associated with variable lipid response such that individuals with the two minor alleles had ~20% smaller reduction in total cholesterol and LDL than individuals with two major alleles of the gene . Our lab recently reported that these two SNPs were also associated with reduced simvastatin efficacy in the Cholesterol and Pharmacogenetics (CAP) study and formed a haplotype (H7) with a third SNP (rs3846662) that was associated with variation in the proportion of HMGCR exon 13 that is alternatively spliced . HMGCR transcripts lacking of exon 13 encodes part of the statin-binding domain of the enzyme. Our results indicate that variation in the production of an HMGCR isoform (exon 13 skipped) with reduced statin sensitivity is a marker of inter-individual differences in low-density lipoprotein cholesterol response to statin treatment . Modulation in pre-mRNA splicing by the targeted therapies have been attempted with promising results. For example, a recent report demonstrated that specific knock-down pre-mRNA of ApoB100, a key player in the development of atherosclerosis, with anti-sense oligonucleotides induced the skipping of exon 27, generating a shorter variant that has been associated with reduced LDL-cholesterol levels . These findings suggest that alternative splicing is a physiologically and clinically relevant regulator of cholesterol metabolism and may be a marker or signal for drug efficacy evaluation. From the therapeutic perspective, the process of alternative splicing is a potential therapeutic target as it may influence the development of human disease.

Conceptos básicos de Biología Molecular

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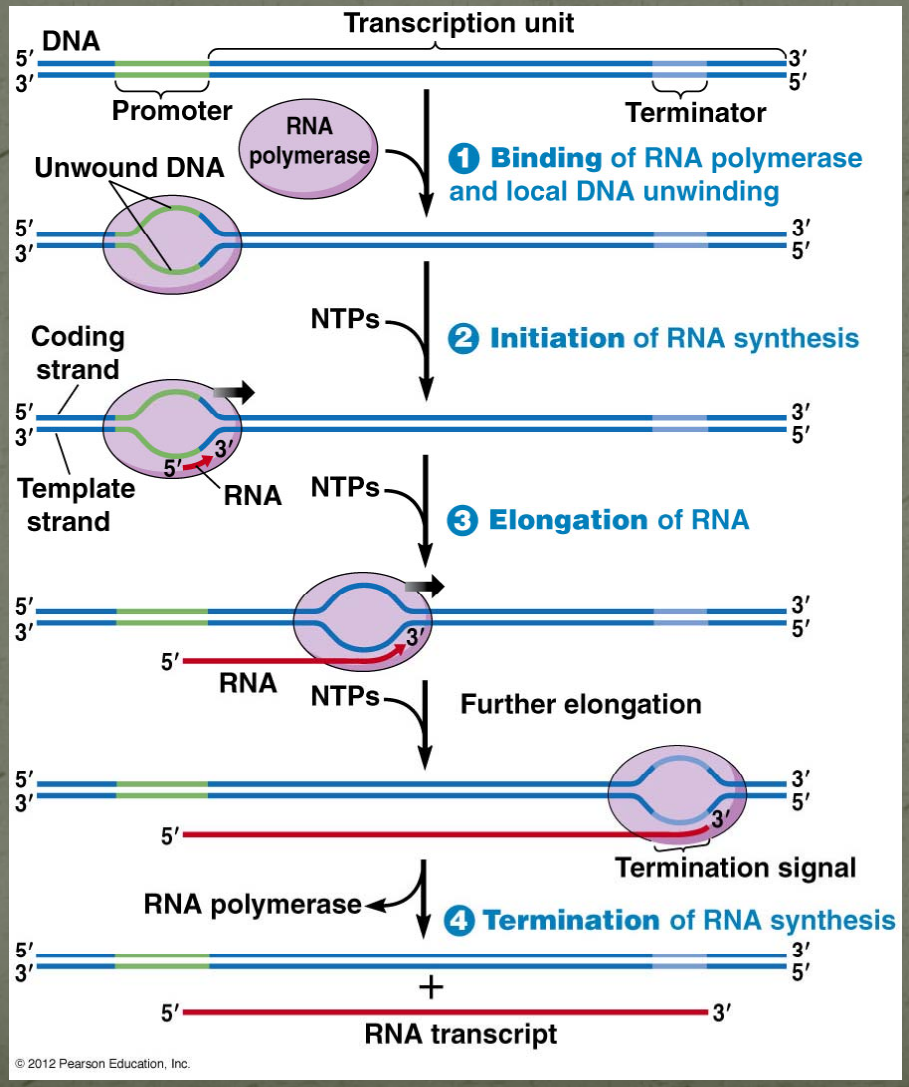

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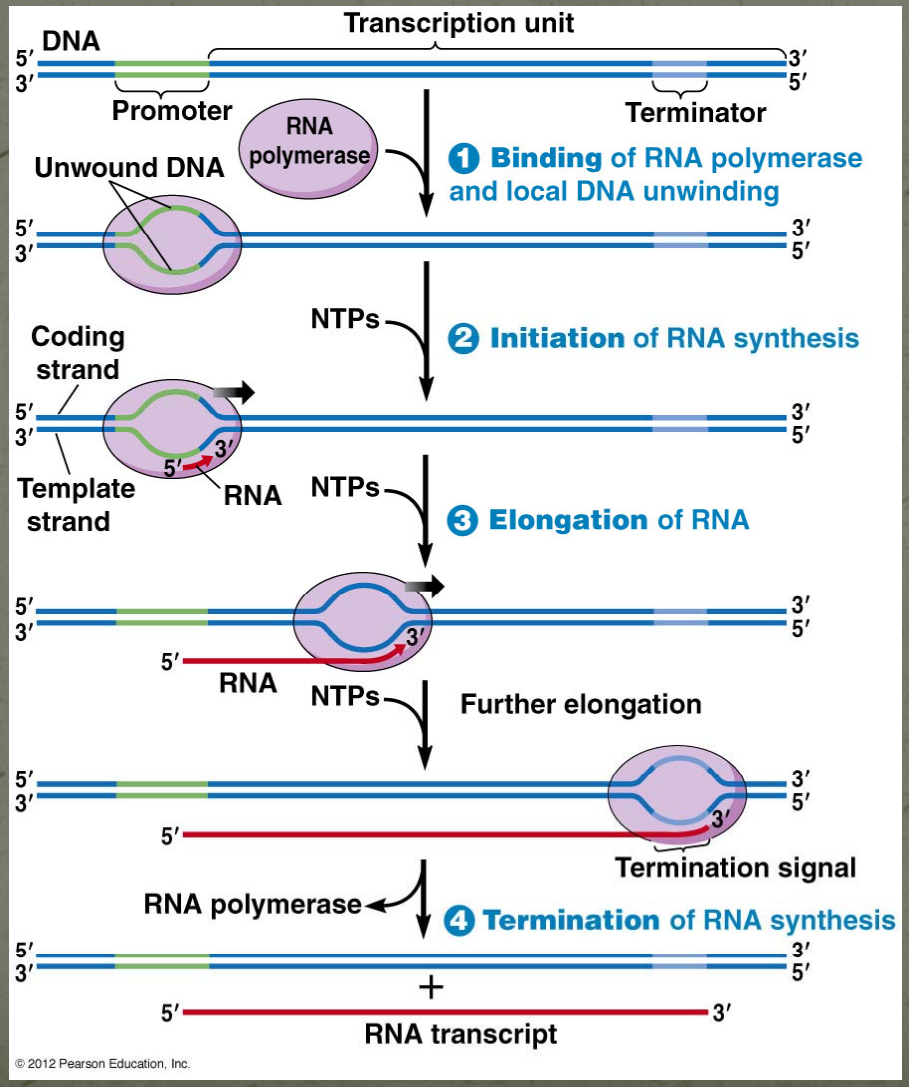

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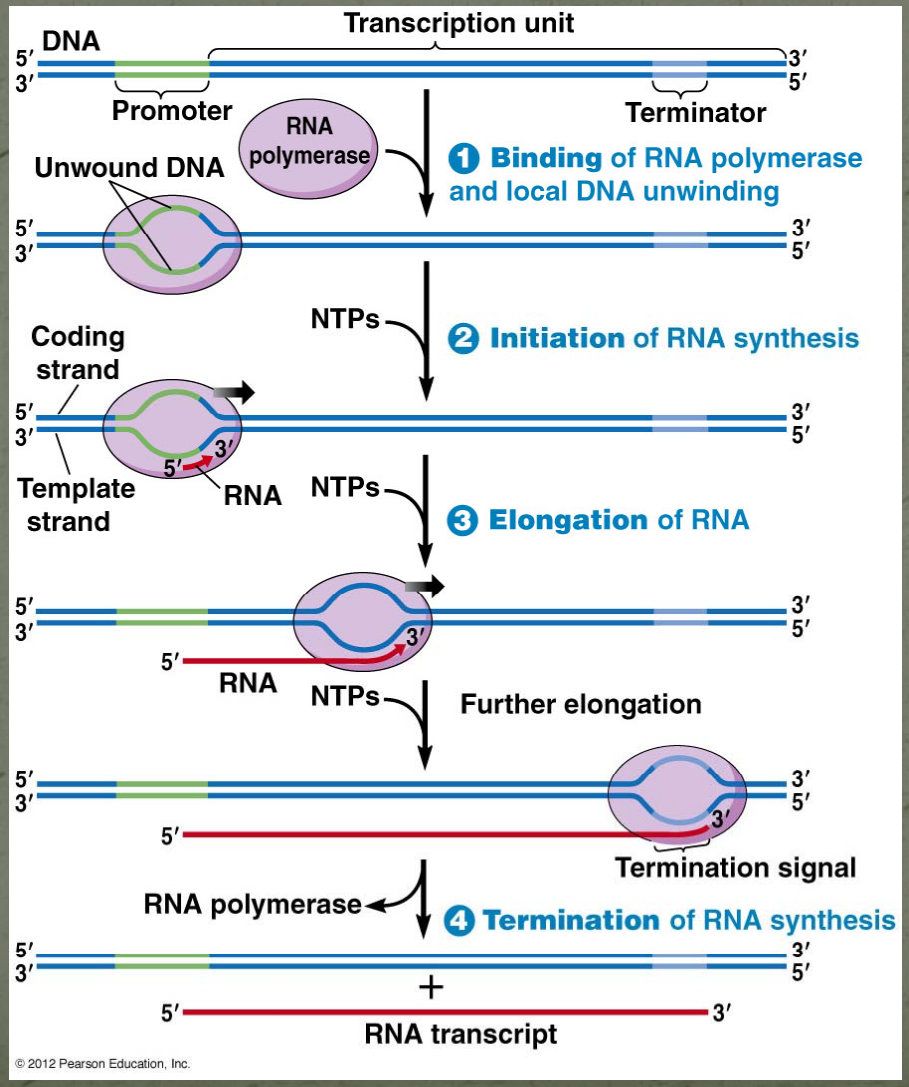

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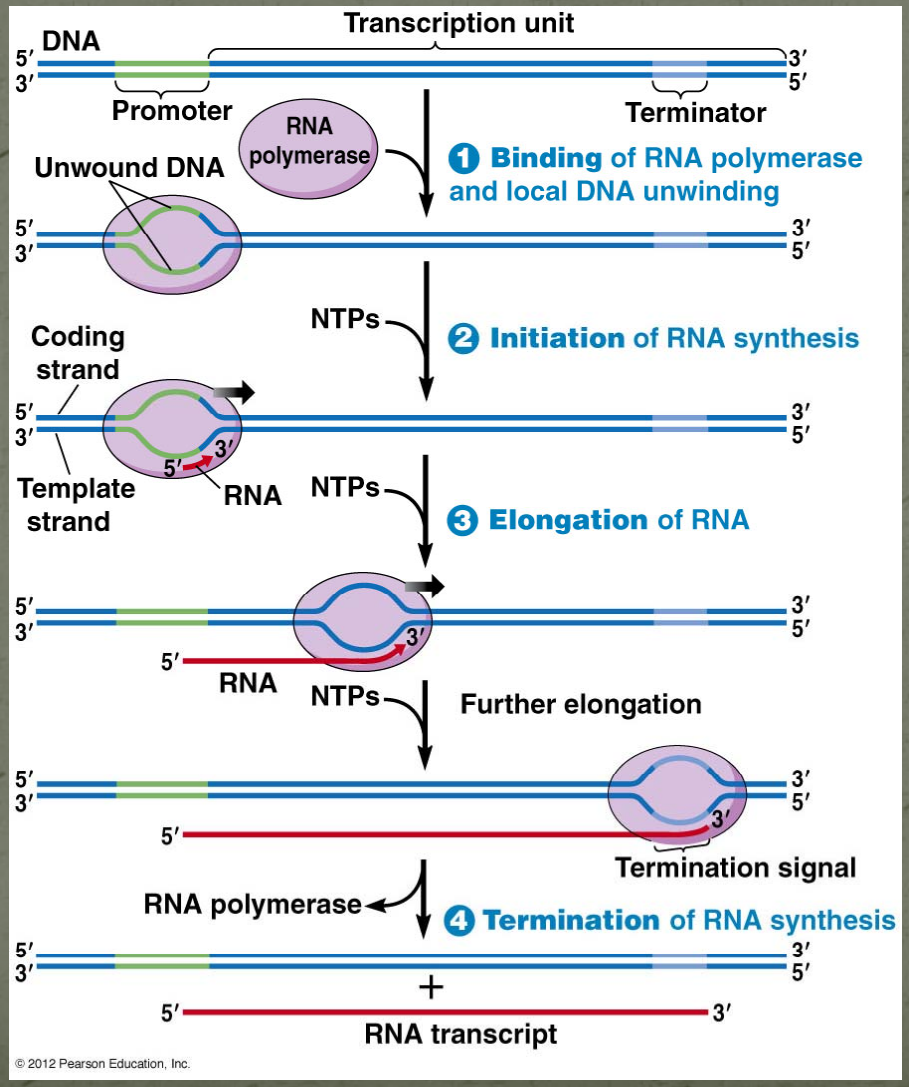

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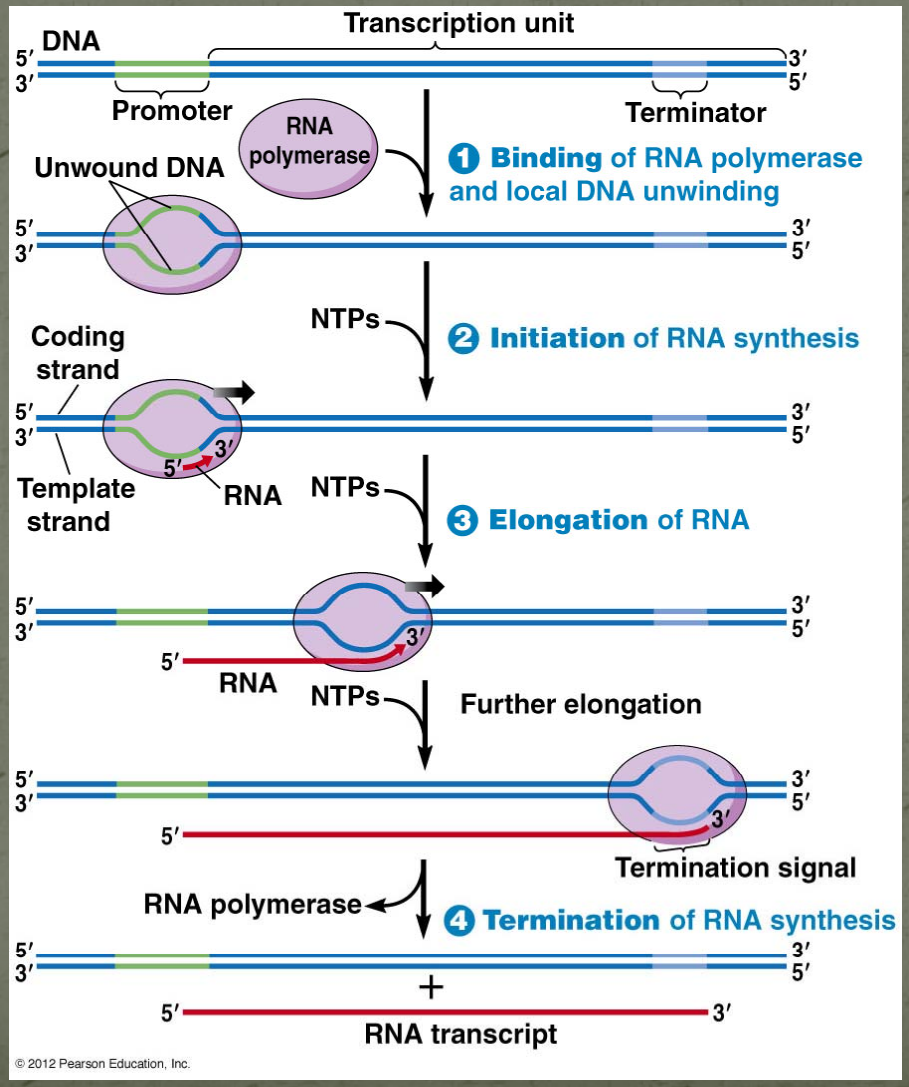

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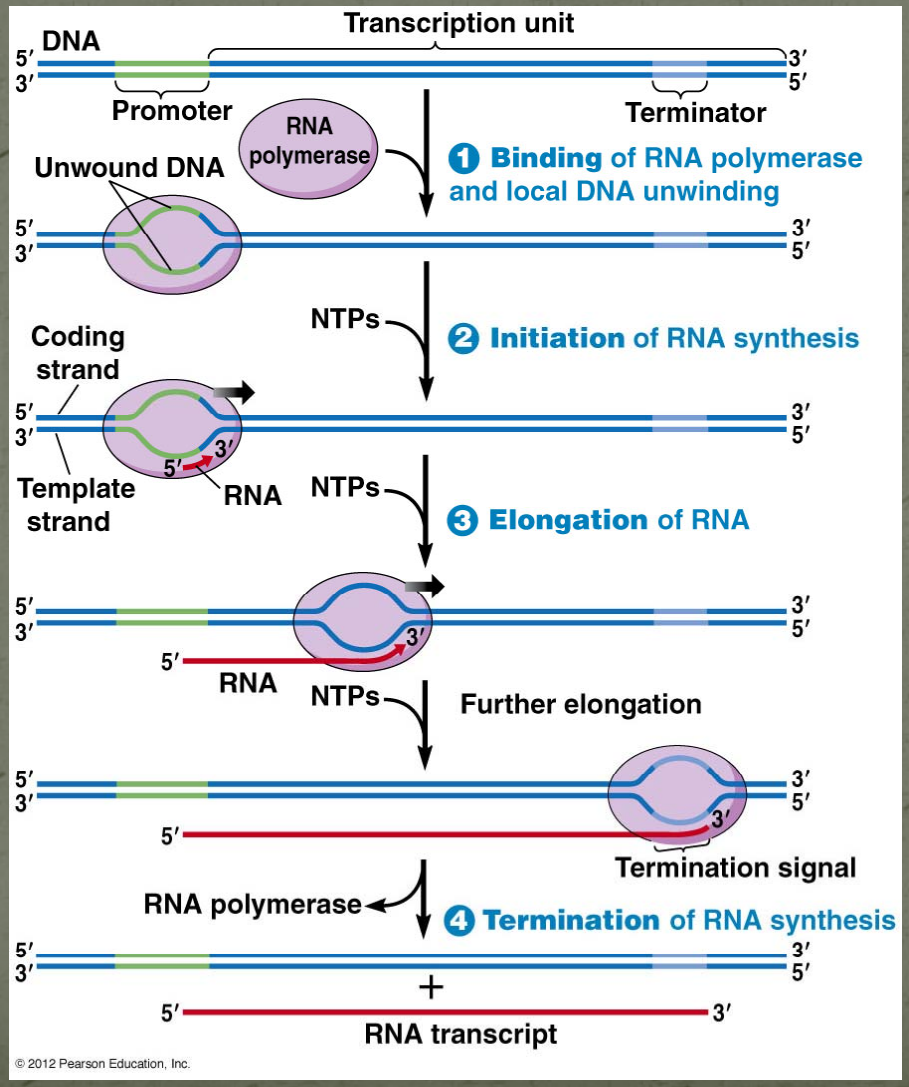

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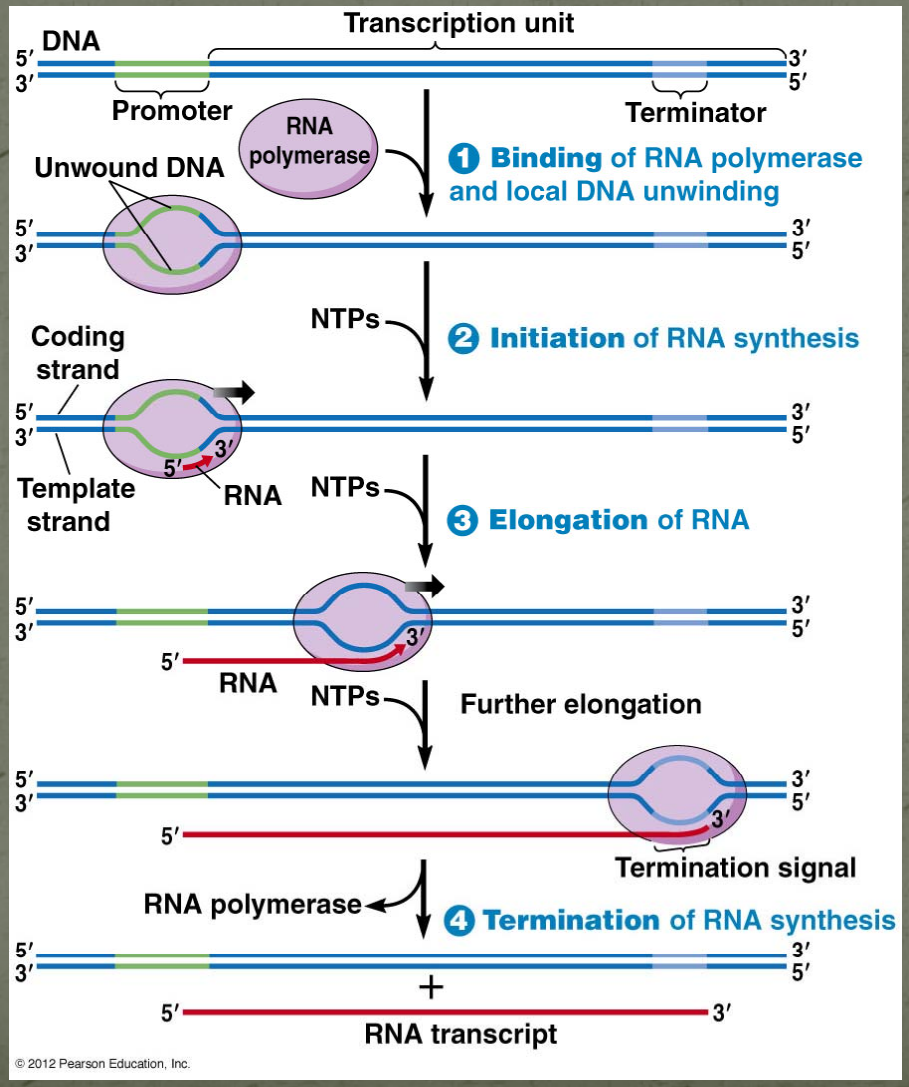

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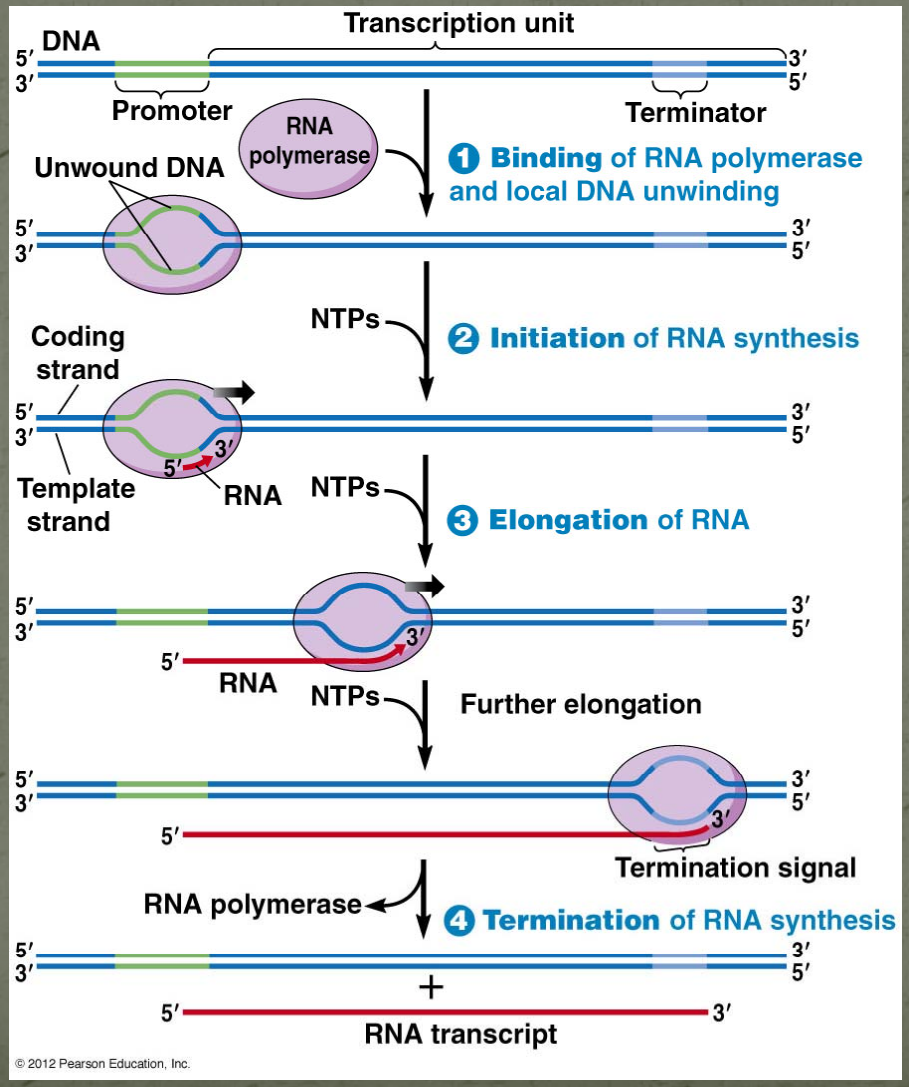

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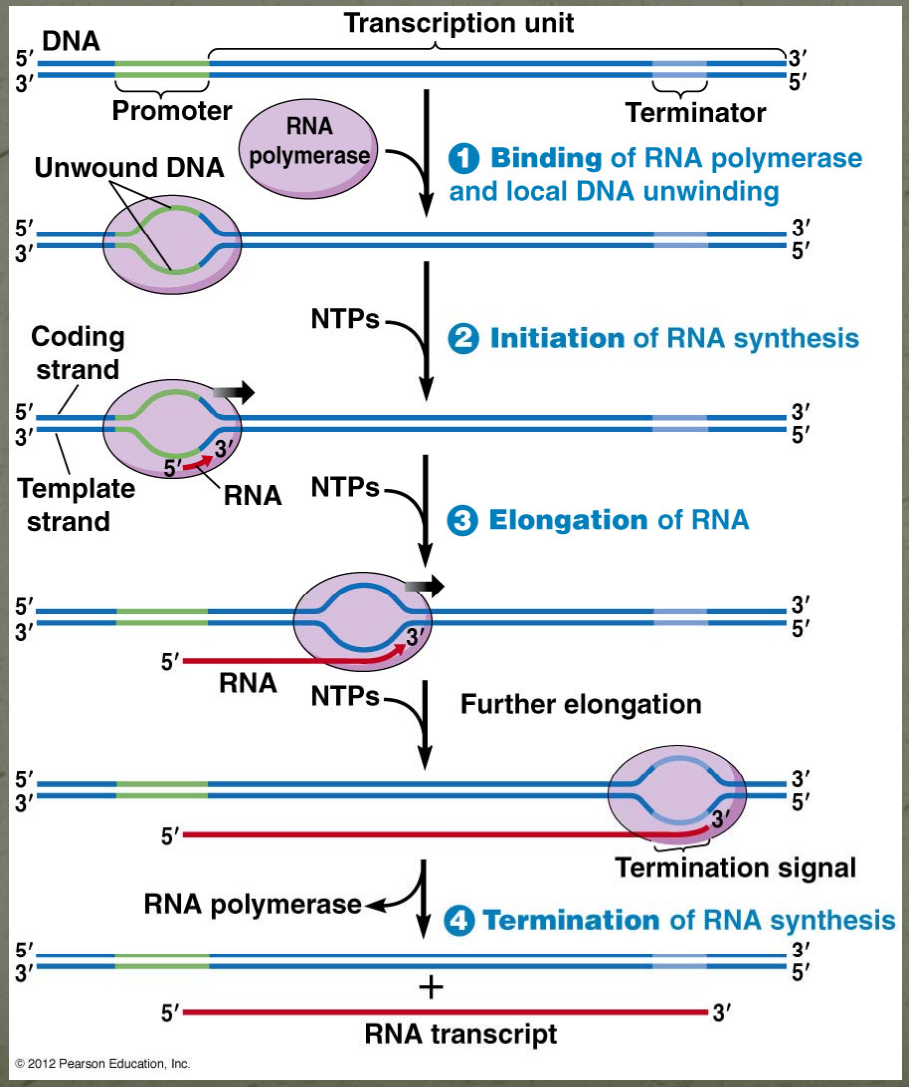
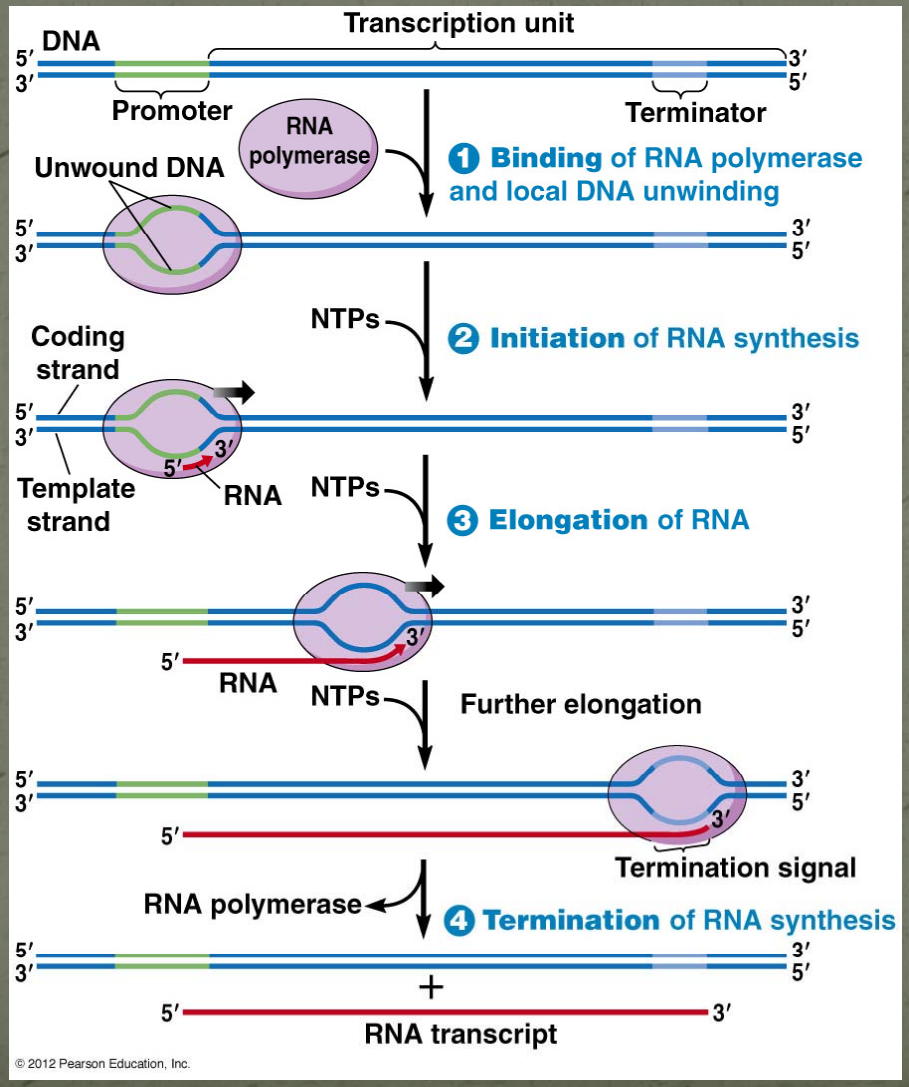


Conceptos básicos de Biología Molecular



Historia del Día de la Tierra

- ¿Cuándo y por qué comenzó el Día de la Tierra?

Actividades del Día de la Tierra

- Hacer aquí una lista de actividades

Sacar a la luz el Día de la Tierra

- Hacer aquí una lista de ideas

Recursos del Día de la Tierra

- Hacer aquí una lista de recursos