生物学基礎I　PART 4 OF 4

転写・翻訳
TRANSCRIPTION AND TRANSLATION

神経遺伝情報学
増田章男
amasuda@med.nagoya-u.ac.jp

DNAの変異はどんな疾患を引き起こすか？

Your answers

鎌状赤血球貧血症、血友病、アルビノ

先天性疾患、フェニルケトン尿症、小人症、巨人症

ハンチントン病、ミトコンドリア症、筋ジストロフィー、色覚異常、

癌、白血病、

ダウン症、ターナー症候群、18トリソミー

糖尿病、アルツハイマー病、パーキンソン病、自閉症、慢性関節リウマチ

免疫異常？

敗血症

ハンセン病？？？

セントラルドグマ

Transcription
転写

Translation
翻訳

DNA
↓
RNA
↓
タンパク質

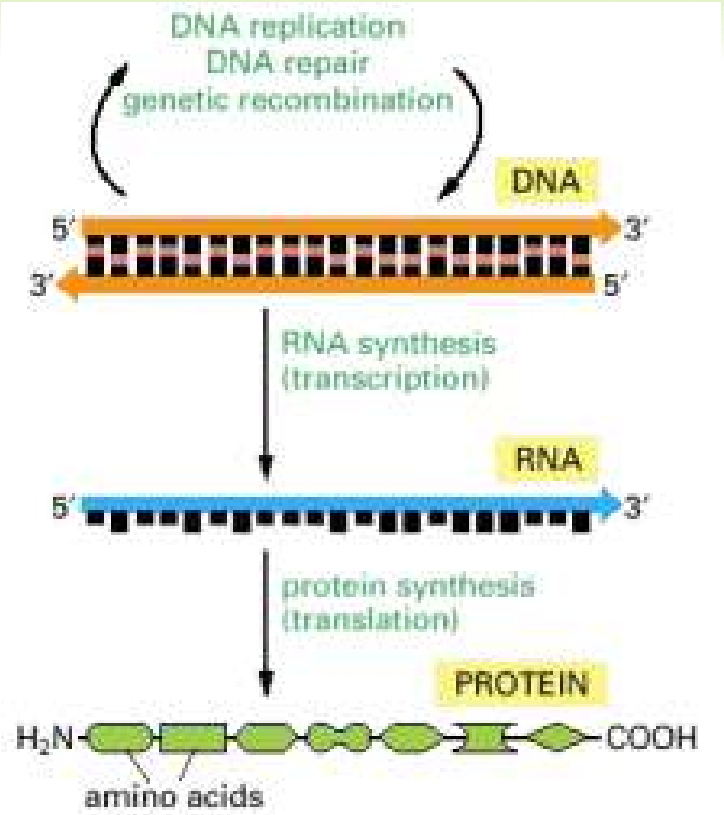
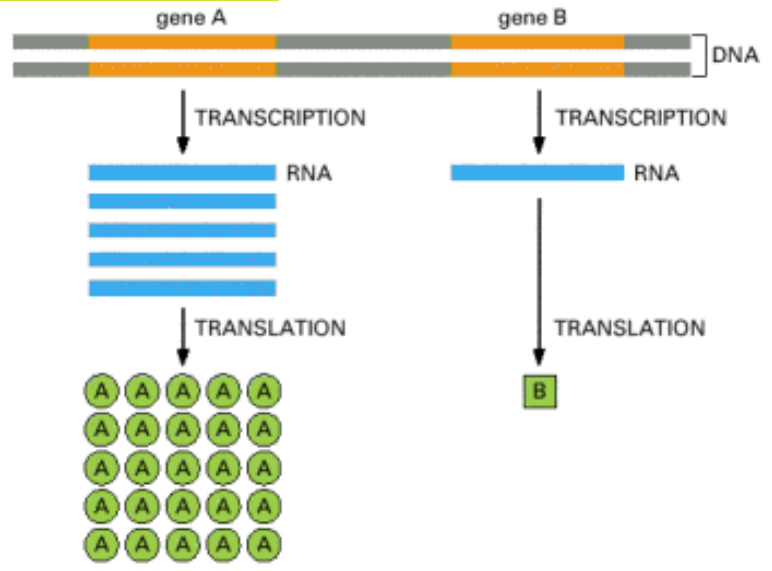


Figure 7-1 *Essential Cell Biology, 1st ed.* (© Garland Science 1998) 212p.

課題

- セントラルドグマ
- 転写・翻訳の機構を理解する

D



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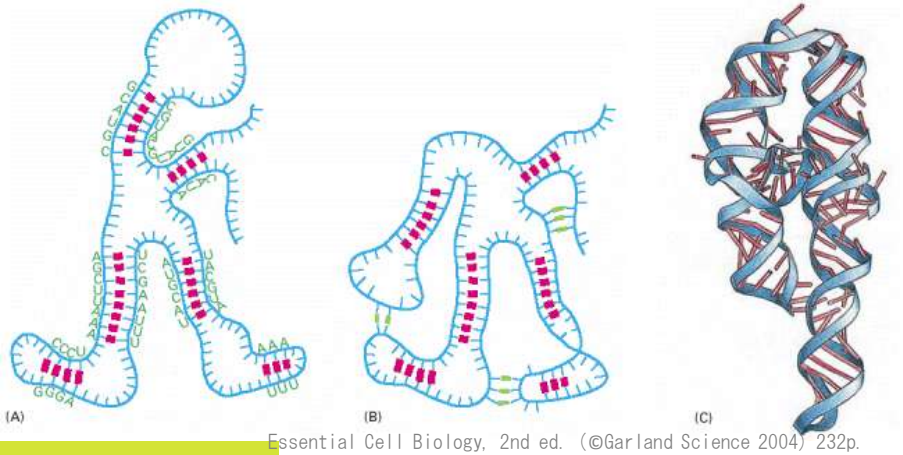

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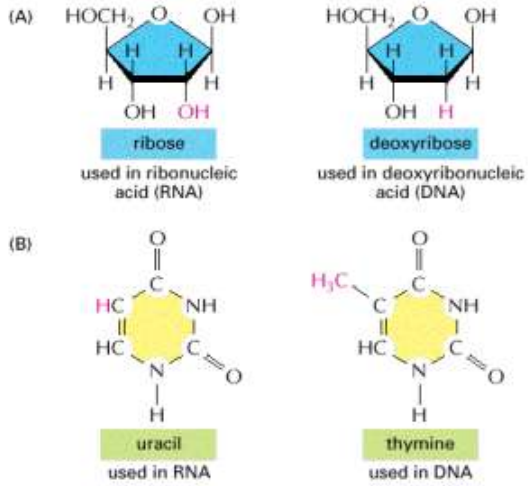

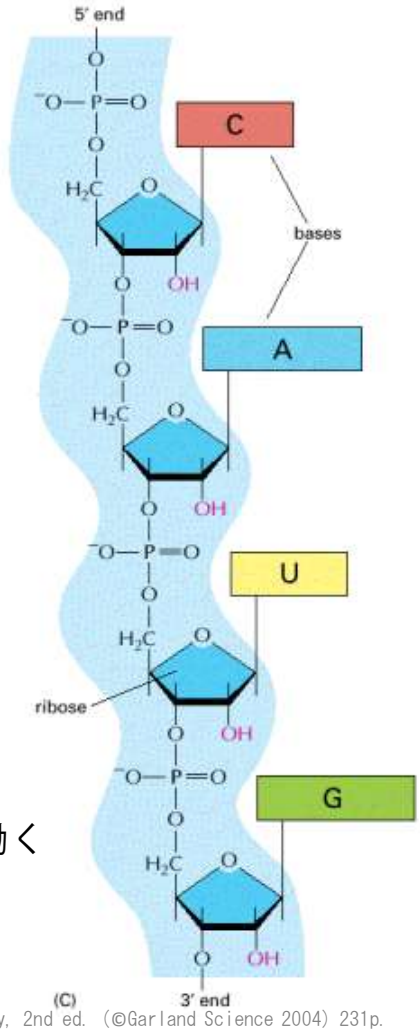

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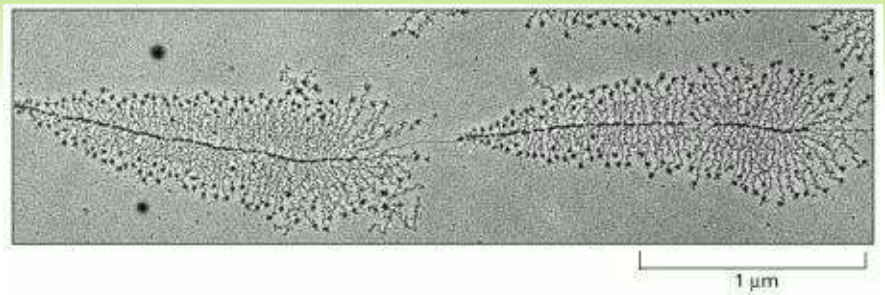
- RNAは原則的に一本鎖で働く
- Transcript 転写産物

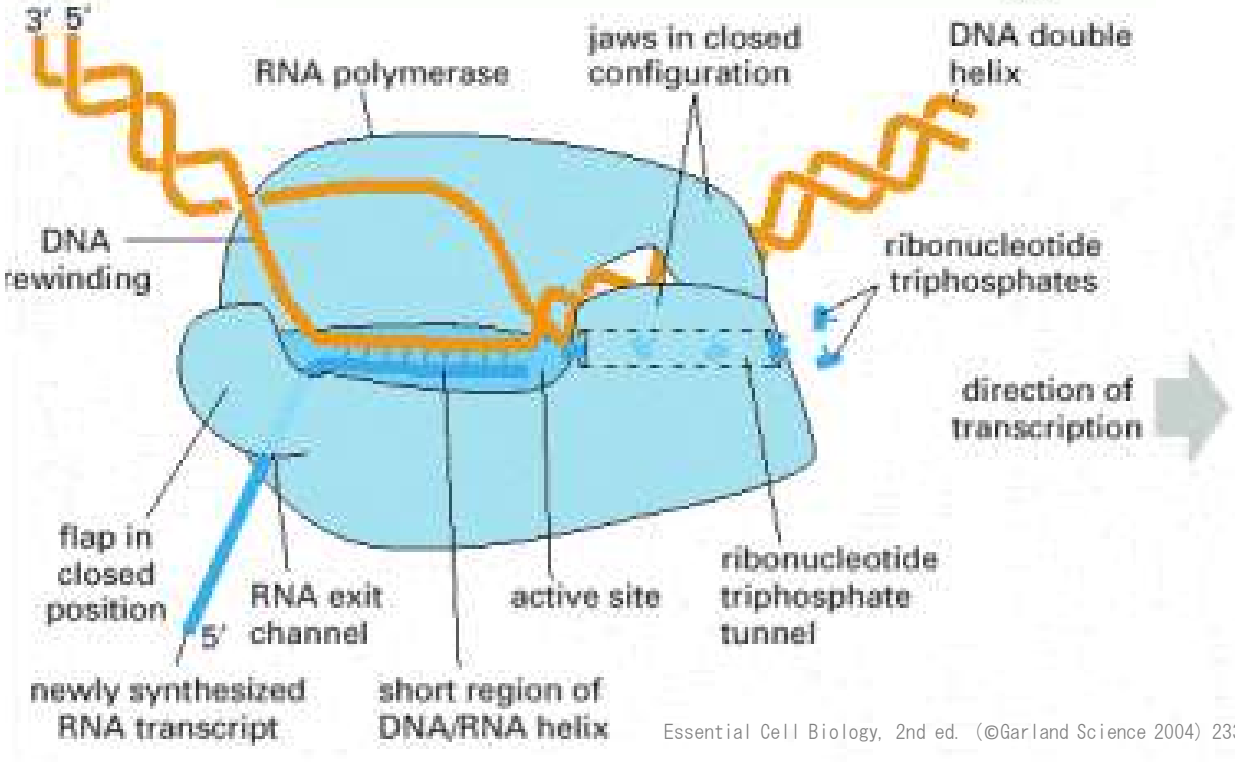
RNAの種類

	Principal Types of RNAs Produced in Cells
mRNAs	messenger RNAs（メッセンジャーRNA）, code for proteins
rRNAs	ribosomal RNAs （リボソームRNA）, form the basic structure of the ribosome and catalyze protein synthesis
tRNAs	transfer RNAs （トランスファーRNA）, central to protein synthesis as adaptors between mRNA and amino acids
snRNAs	small nuclear RNAs, function in a variety of nuclear processes, including the splicing of pre-mRNA
snoRNAs	small nucleolar RNAs, used to process and chemically modify rRNAs
Other noncoding RNAs	function in diverse cellular processes, including telomere synthesis, X-chromosome inactivation, and the transport of proteins into the ER

RNAの合成

- RNA polymerase RNAポリメラーゼ
- RNA polymeraseのerror rate $1/10^4$
- (DNA polymeraseのerror rate $1/10^7$)
- RNA polymeraseはprimerを必要としない
- RNA合成材料NTP (ATP, CTP, UTP, GTP)





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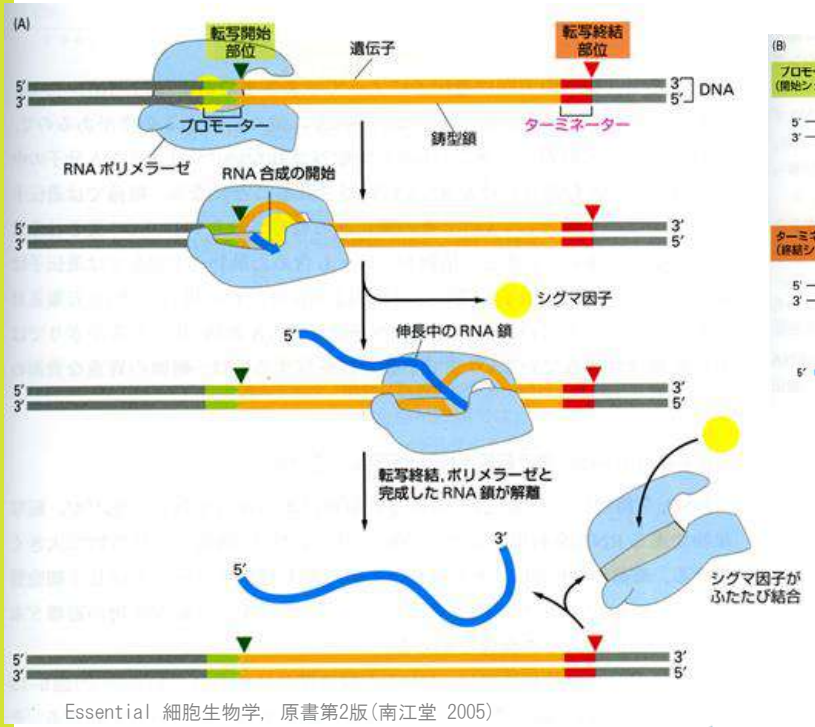
RNA POLYMERASE

- RNA polymerase I
  - Ribosome RNA
- RNA polymerase II
  - 蛋白をcodeするRNA
- RNA polymerase III
  - snoRNA

細菌でのRNA合成

シグマ因子
プロモーター
ターミネーター



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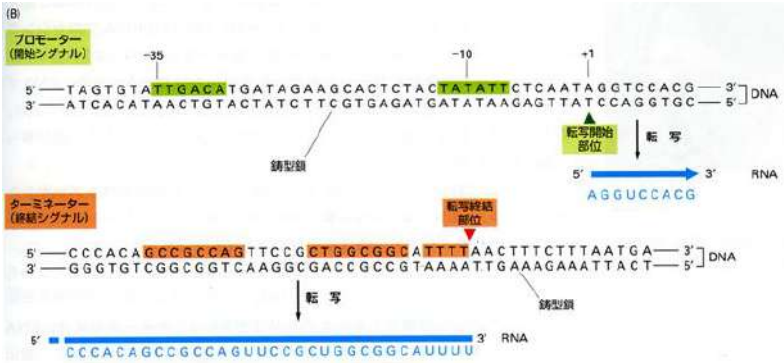

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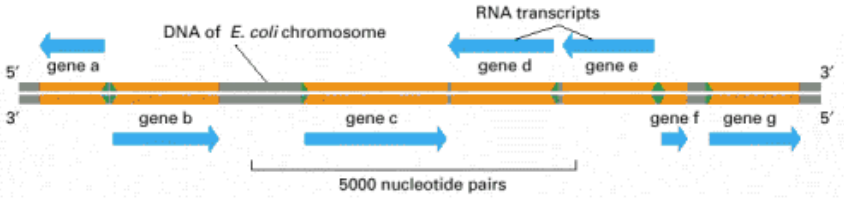

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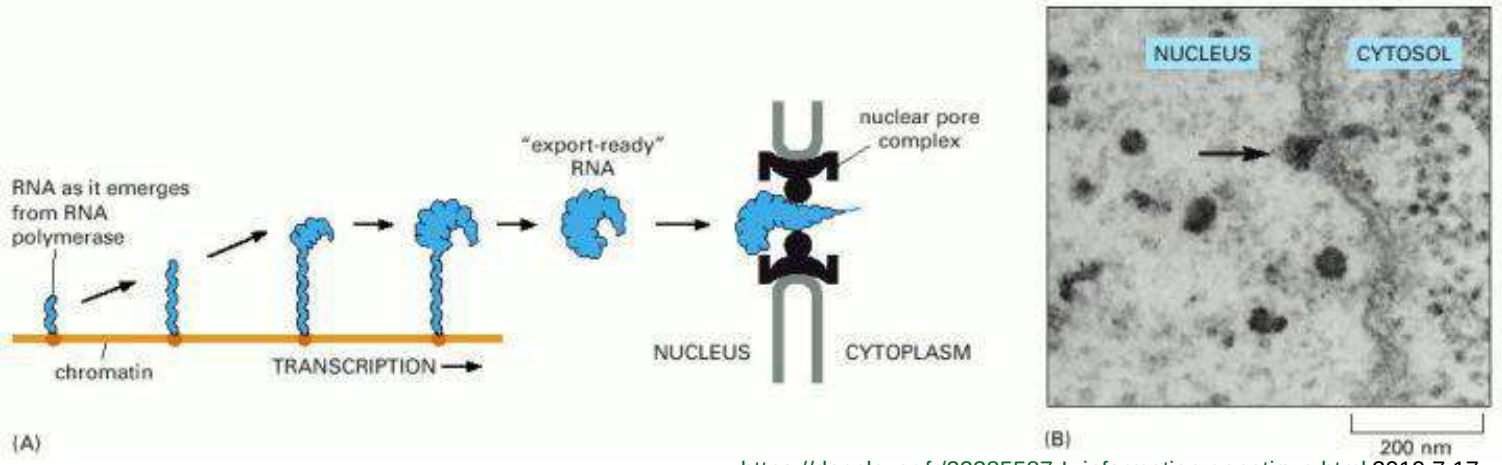
真核生物でのRNA合成

- 転写は核内で起こる
- RNAはプロセシングを経て、核外へ輸送される
- 細胞質でタンパク合成を行う

•Nuclear Pore Complex 核膜孔複合体



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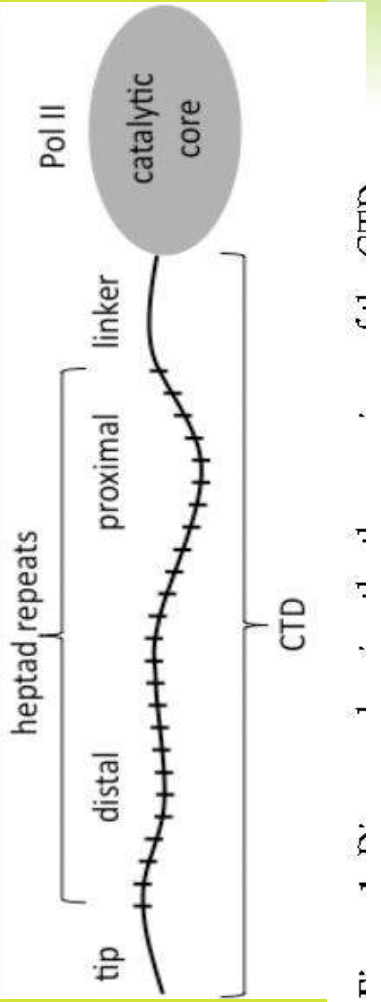
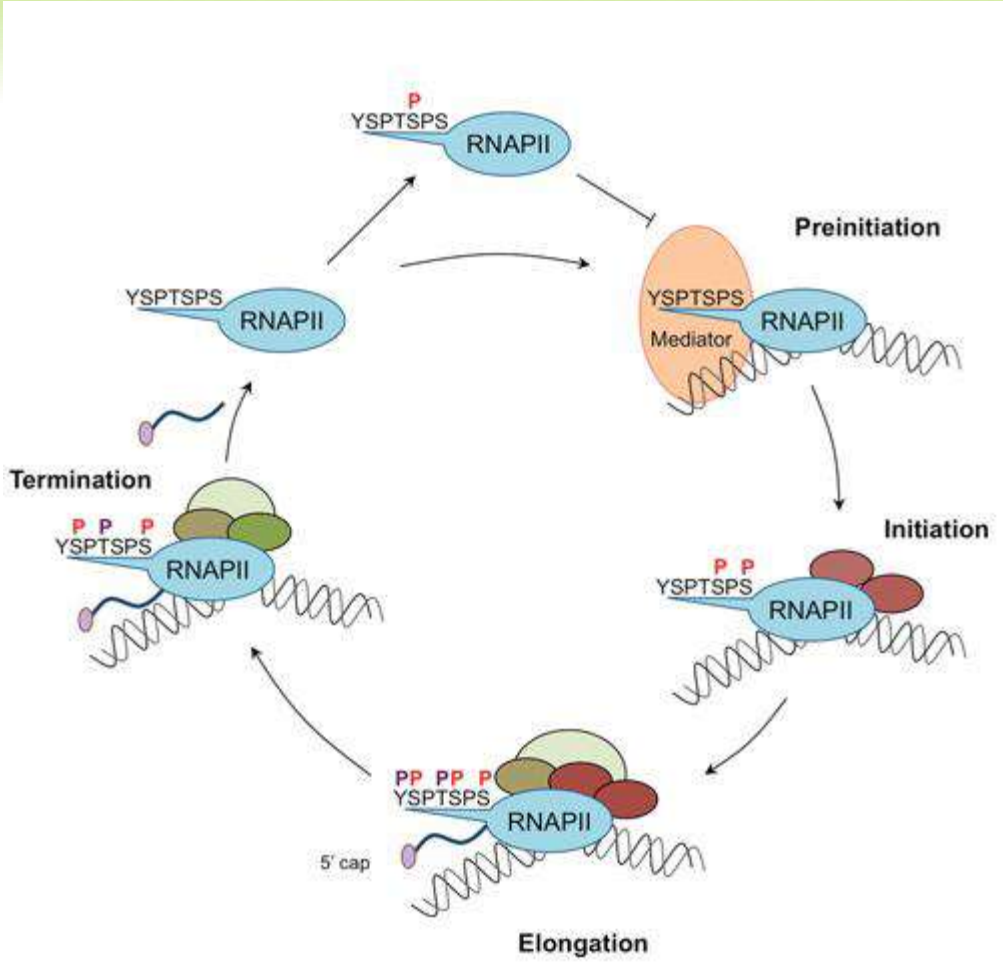
RNA POLYMERASE II



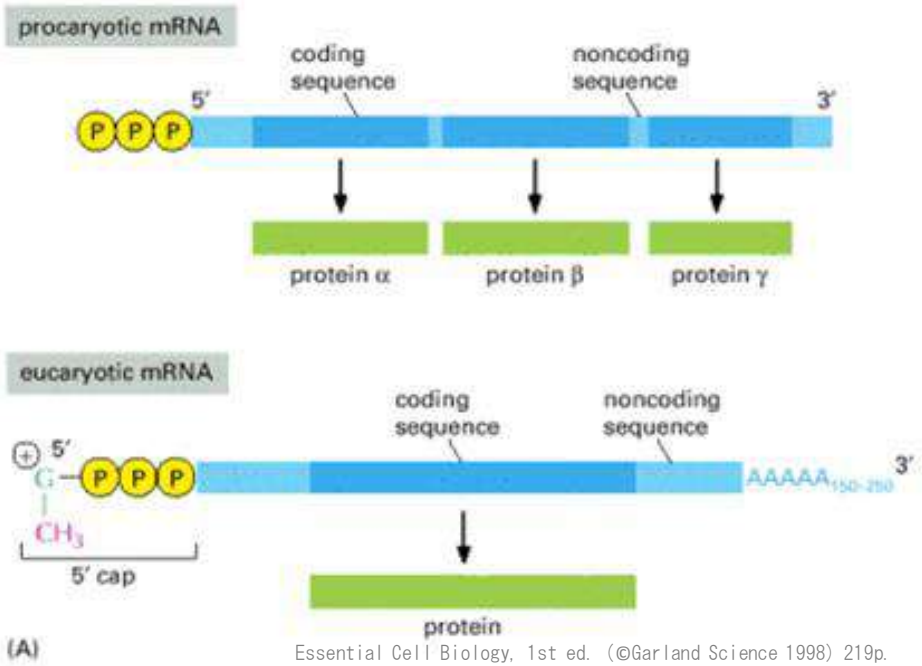
https://www.semanticscholar.org/paper/RNA-polymerase-II-C-terminal-domain%3A-Tethering-to-Corden/eb2ab45f05debce139c3d2181098c6e4d66d449d 2019.7.17



https://www.researchgate.net/figure/Dynamic-CtD-phosphorylation-patterns-during-the-RNAP-ii-transcription-cycle-RNA_fig1_230837755 2019.7.17

mRNAはCAP形成とポリアデニル化をうける

- Polycistronic　vs　monocistronic
- RNA Capping　RNAキャップ形成
- Polyadenylation　ポリアデニル化
- Polyadenylation signal　AAUAAA



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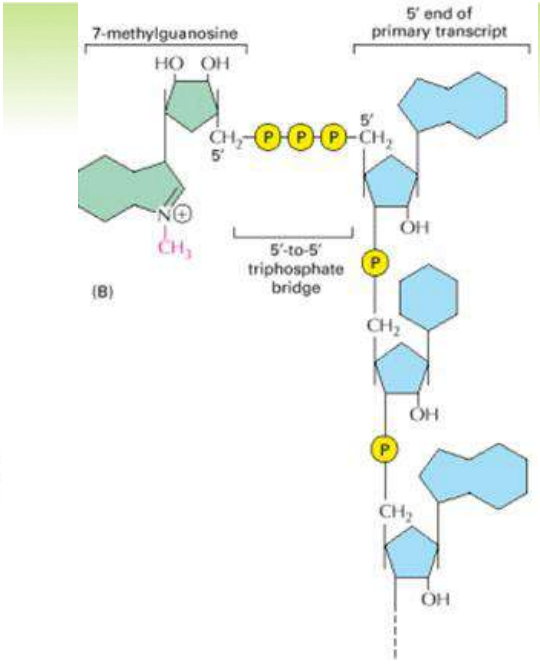

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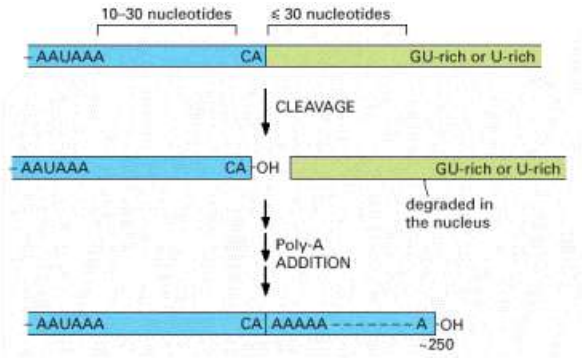
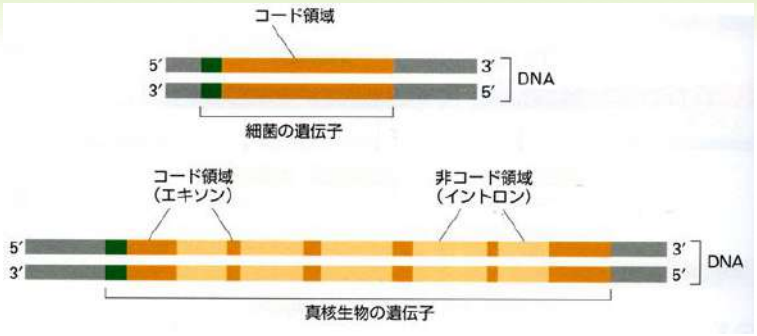


mRNAの安定性を高める
核から細胞質への輸送を助ける
タンパク合成の効率が高まる

mRNAであることの目印

スプライシング

- Pre-mRNA splicing
  スプライシング
- Exon
  エキソン
- Intron
  イントロン
- RNA Processing RNA
  プロセッシング
- Pre-mRNA splicing
  スプライシング



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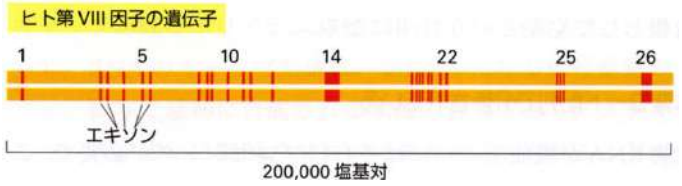

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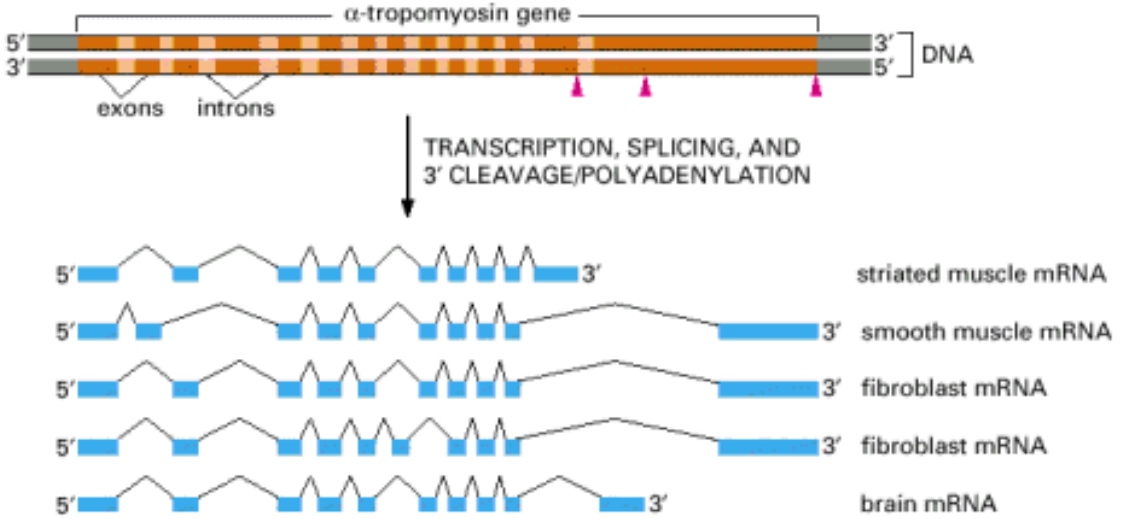

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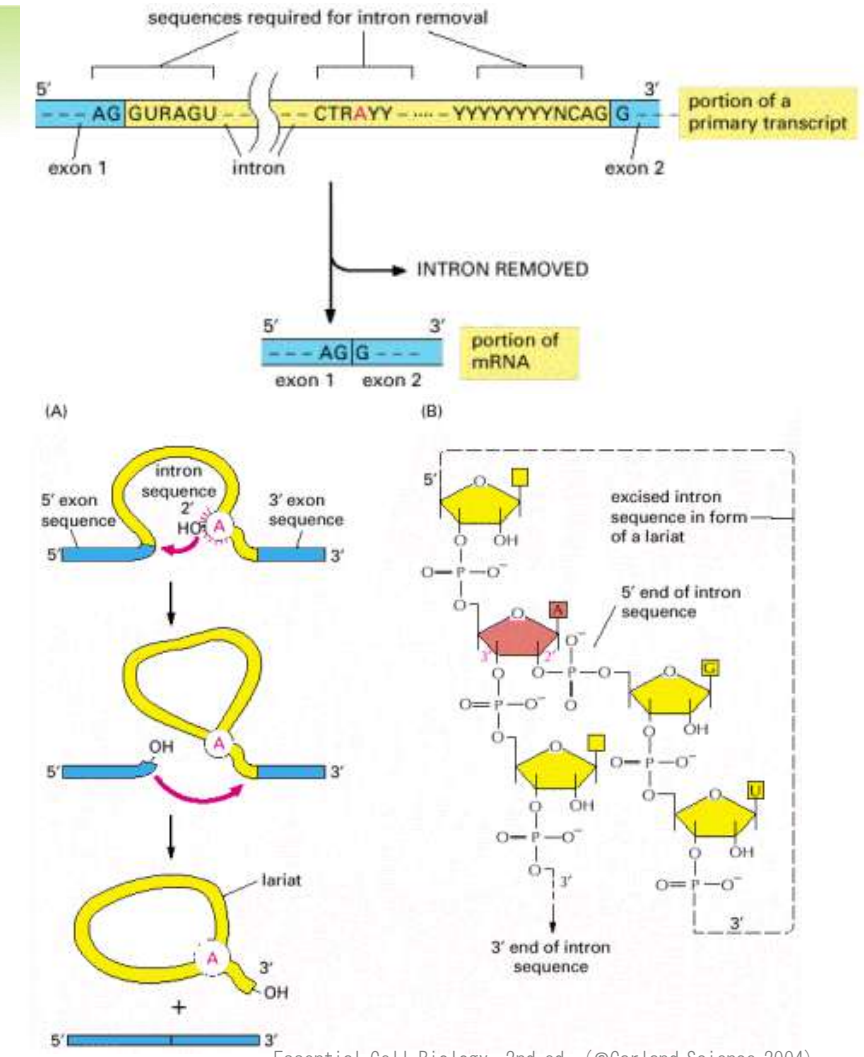
スプライシング制御

- Small nuclear RNA (snRNA)
- Small nuclear ribonucleoproteins (snRNPs)
- Spliceosome
  スプライソソーム
- Lariat
  ラリアート

- スプライスは、RNA分子によって制御される！



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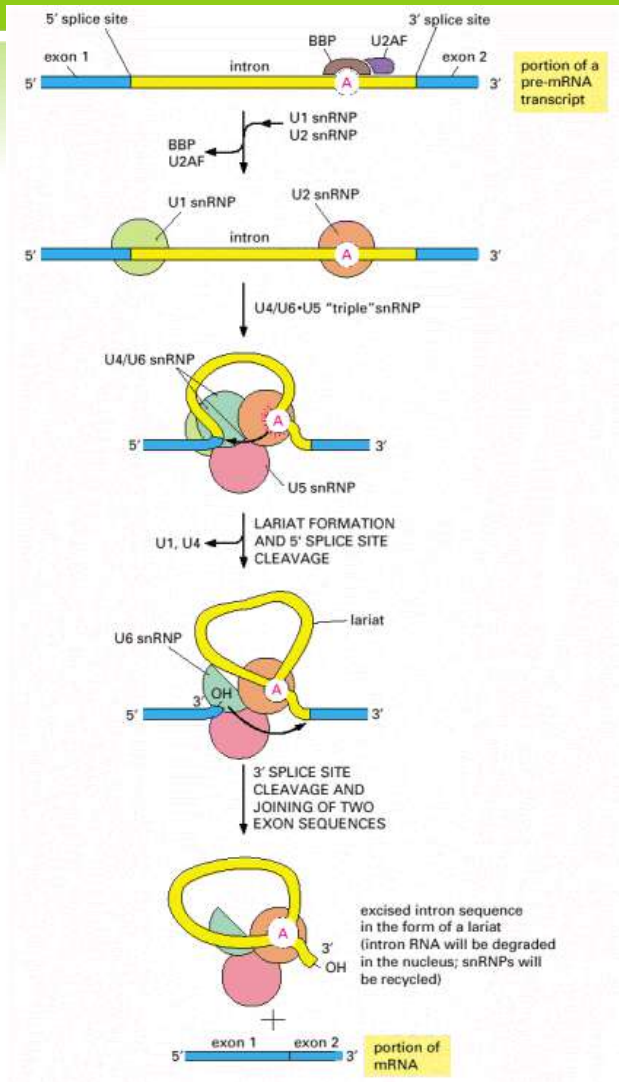

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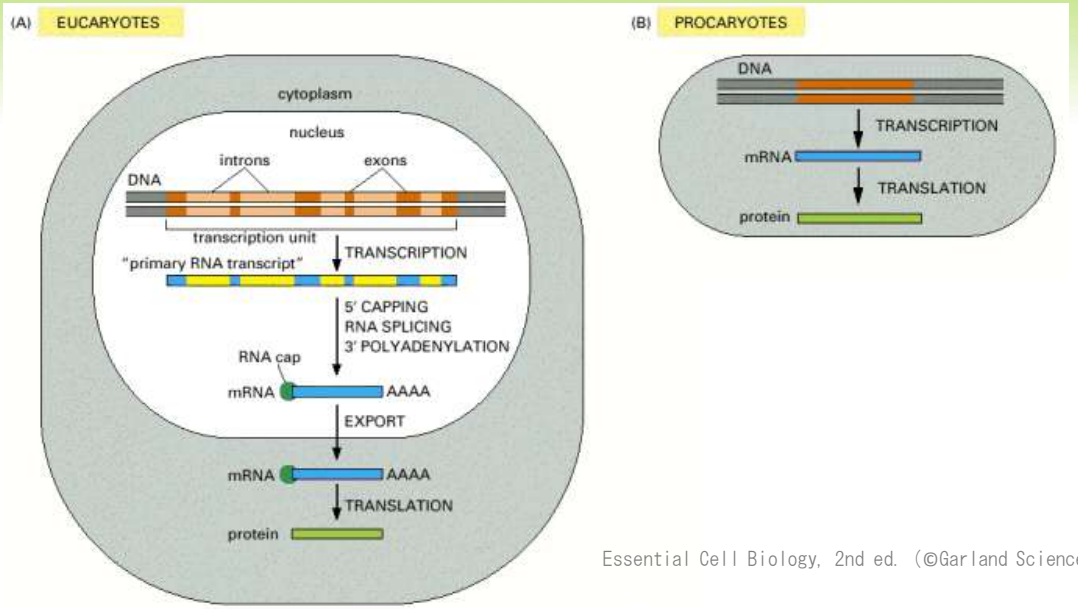
RNAは輸送の過程で選別される

- Cap binding complex (CBC)
- Poly-A-binding protein (PABP)
- Exon junction complex (EJC)



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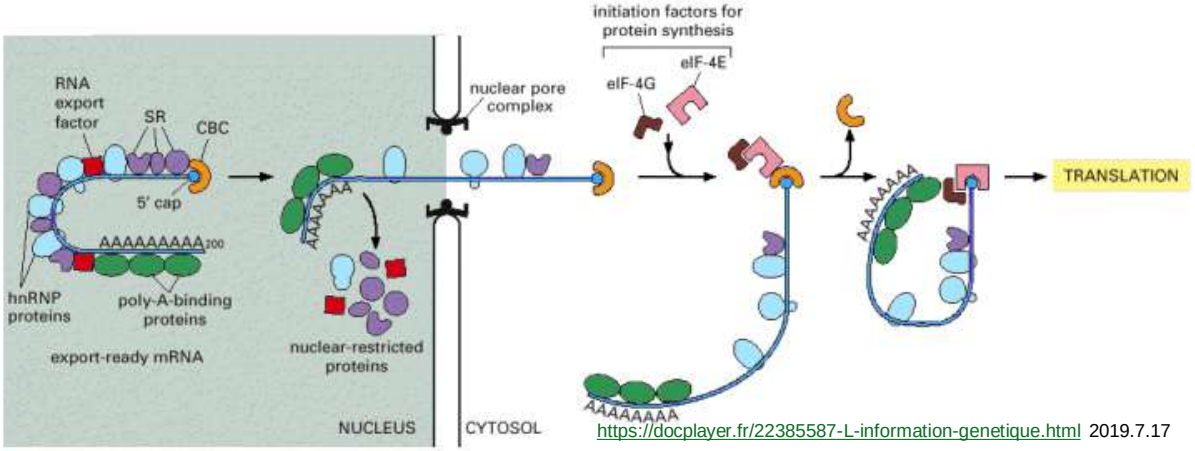

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最終的に、mRNAは細胞内で分解される。寿命は、細菌で3分。真核生物で、30分から10時間程度。

RNAからタンパク質へ

- Genetic code 遺伝暗号
- Codon コドン
- Reading frame リーディングフレーム

GCA GCC GCG GCU	AGA AGG CGA CGC CGG CGU	GAC GAU	AAC AAU	UGC UGU	GAA GAG	CAA CAG	GGA GGC GGG GGU	CAC CAU	AUA AUC AUU	UUA UUG CUA CUC CUG CUU	AAA AAG	AUG	UUC UUU	CCA CCC CCG CCU	AGC AGU UCA UCC UCG UCU	ACA ACC ACG ACU	UGG	UAC UAU	GUA GUC GUG GUU	UAA UAG UGA
Ala	Arg	Asp	Asn	Cys	Glu	Gln	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val	終止
A	R	D	N	C	E	Q	G	H	I	L	K	M	F	P	S	T	W	Y	V	

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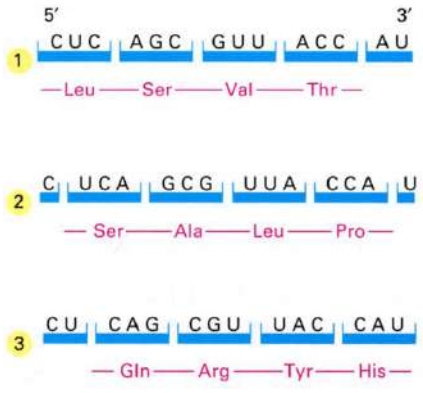
First	Second				Third
	Uracil (U)	Cytosine (C)	Adenine (A)	Guanine (G)	
Uracil (U)	F Phenylalanine (Phe)	S Serine (Ser)	Y Tyrosine (Tyr)	C Cysteine (Cys)	U
	F Phenylalanine (Phe)	S Serine (Ser)	Y Tyrosine (Tyr)	C Cysteine (Cys)	C
	L Leucine (Leu)	S Serine (Ser)	Stop Codon	Stop Codon	A
	L Leucine (Leu)	S Serine (Ser)	Stop Codon	W Tryptophan (Trp)	G
Cytosine (C)	L Leucine (Leu)	P Proline (Pro)	H Histidine (His)	R Arginine (Arg)	U
	L Leucine (Leu)	P Proline (Pro)	H Histidine (His)	R Arginine (Arg)	C
	L Leucine (Leu)	P Proline (Pro)	Q Glutamine (Gln)	R Arginine (Arg)	A
	L Leucine (Leu)	P Proline (Pro)	Q Glutamine (Gln)	R Arginine (Arg)	G
Adenine (A)	I Isoleucine (Ile)	T Threonine (Thr)	N Asparagine (Asn)	S Serine (Ser)	U
	I Isoleucine (Ile)	T Threonine (Thr)	N Asparagine (Asn)	S Serine (Ser)	C
	I Isoleucine (Ile)	T Threonine (Thr)	K Lysine (Lys)	R Arginine (Arg)	A
	Start (Methionine)	T Threonine (Thr)	K Lysine (Lys)	R Arginine (Arg)	G
Guanine (G)	V Valine (Val)	A Alanine (Ala)	D Aspartic acid (Asp)	G Glycine (Gly)	U
	V Valine (Val)	A Alanine (Ala)	D Aspartic acid (Asp)	G Glycine (Gly)	C
	V Valine (Val)	A Alanine (Ala)	E Glutamic acid (Glu)	G Glycine (Gly)	A
	V Valine (Val)	A Alanine (Ala)	E Glutamic acid (Glu)	G Glycine (Gly)	G



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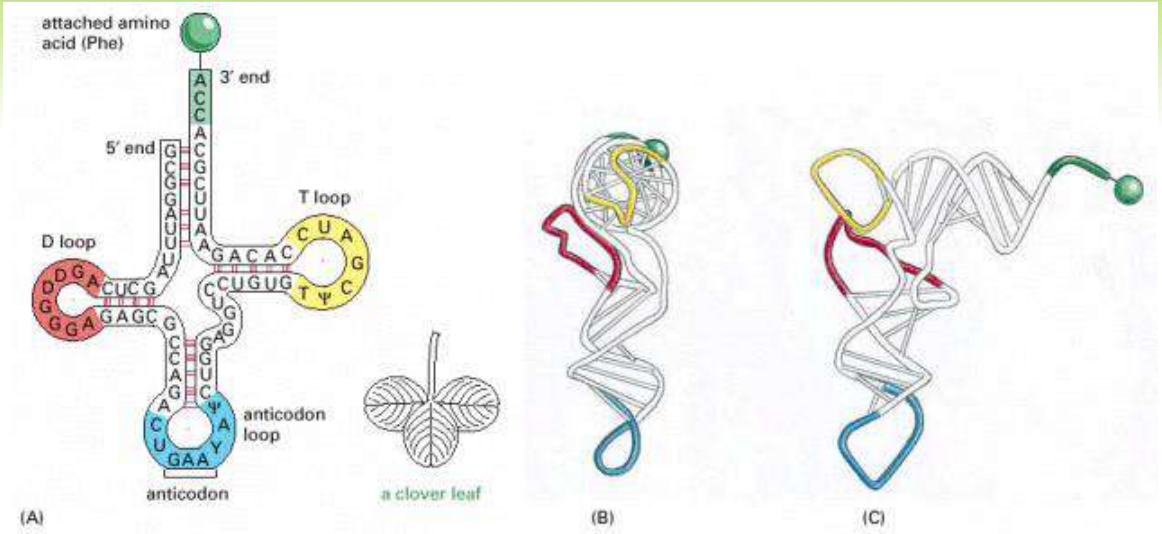
TRANSFER RNA (tRNA)

- Anticodon アンチコドン
- Wobble position
- 3’ end of tRNA is always 5’-CCA-3’
- Dihydrouridine (D)
- Pseudouridine (Ψ)
- ヒトでは497種類のtRNAsに48種類のanticodonsがあり、20種類のアミノ酸をコードしている。



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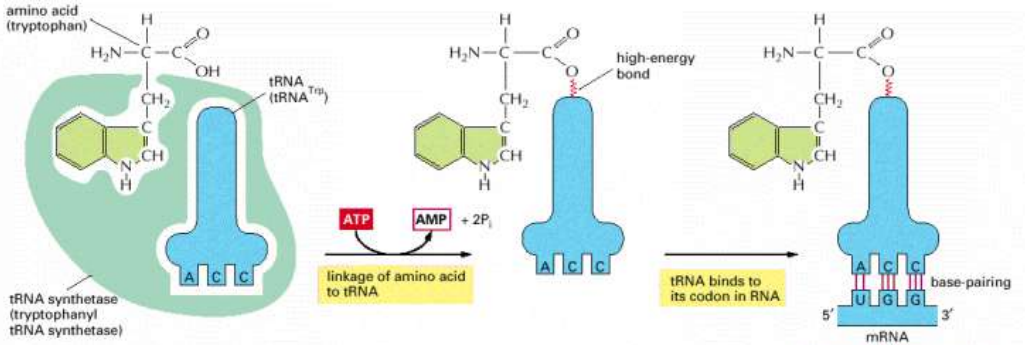

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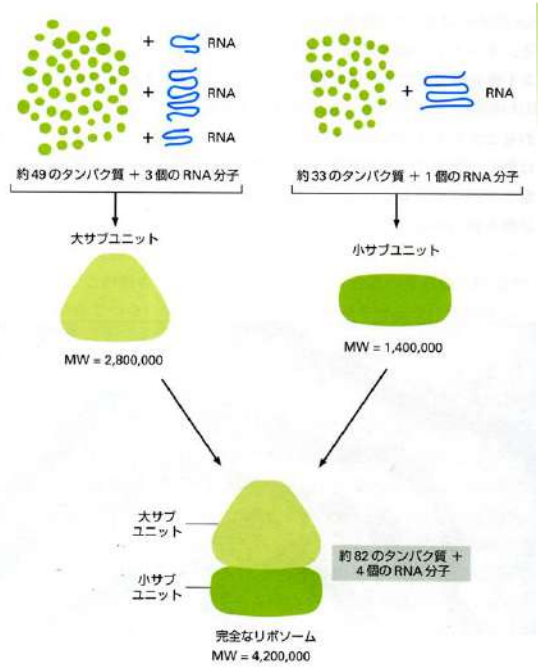
- 20種類のAminoactyl-tRNA synthetase アミノアシルtRNA合成酵素

RIBOSOMAL RNA (r RNA)

- リボソームはタンパク製造装置で、細胞内には数万個のリボソームが存在する。
- リボソームはribosomal proteinsとribosomal RNAs (rRNAs)からなる大型複合体
- Peptidyl transferase ペプチジル基転移酵素



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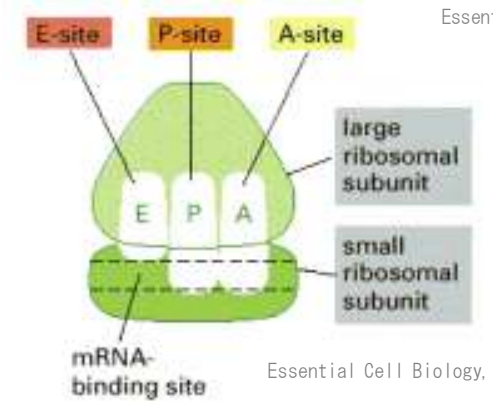

大サブユニット:
アミノ酸間にペプチド結合を形成

小サブユニット:
tRNAをmRNAのコドンに結合

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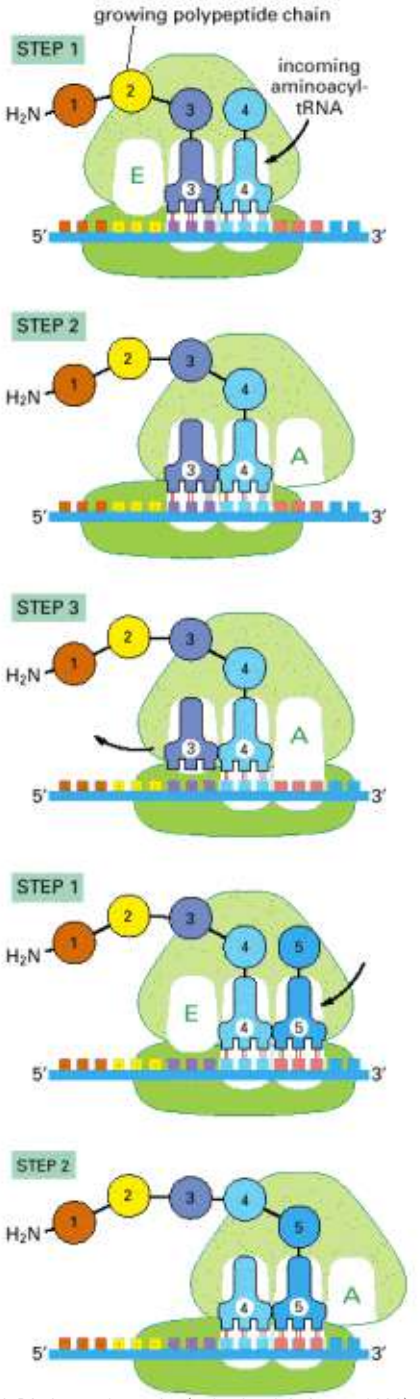

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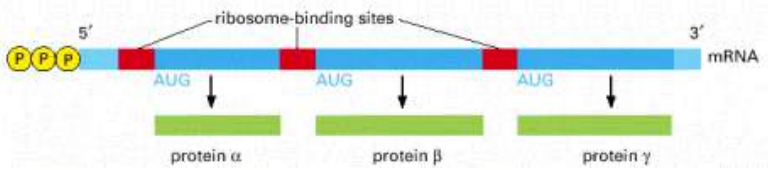
翻訳の開始と終止

- translation initiation factor　　翻訳開始因子
- 翻訳開始は必ずAUGコドンで、initiator tRNA（開始tRNA）に結合をしたメチオニン(真核細胞)かホルミルメチオニン（原核細胞）
- Eucaryoteでは5’ cap、procaryoteではribosomal binding site (RBS)からスキャンニングを開始
- Releasing factor 終結因子
- Polyribosome ポリリボソーム（polysome ポリソーム）　80塩基間隔



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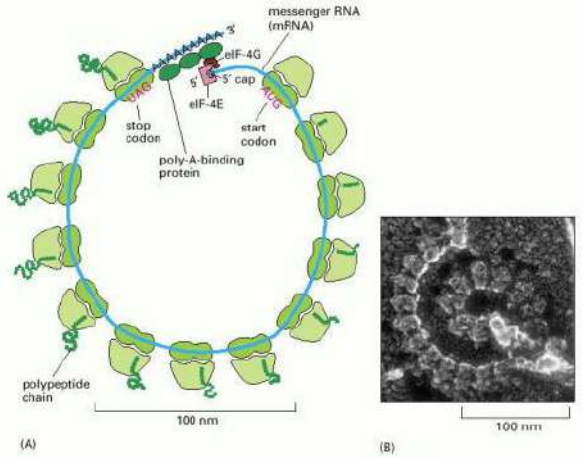

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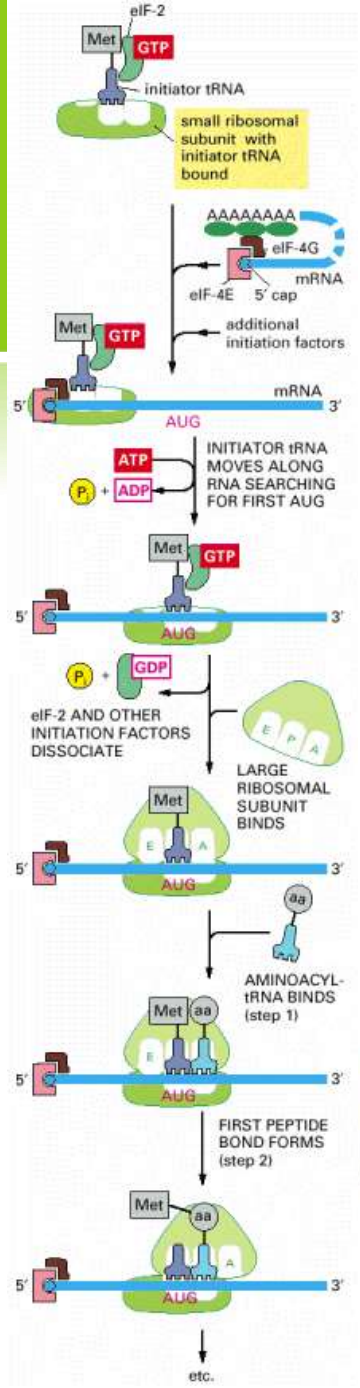

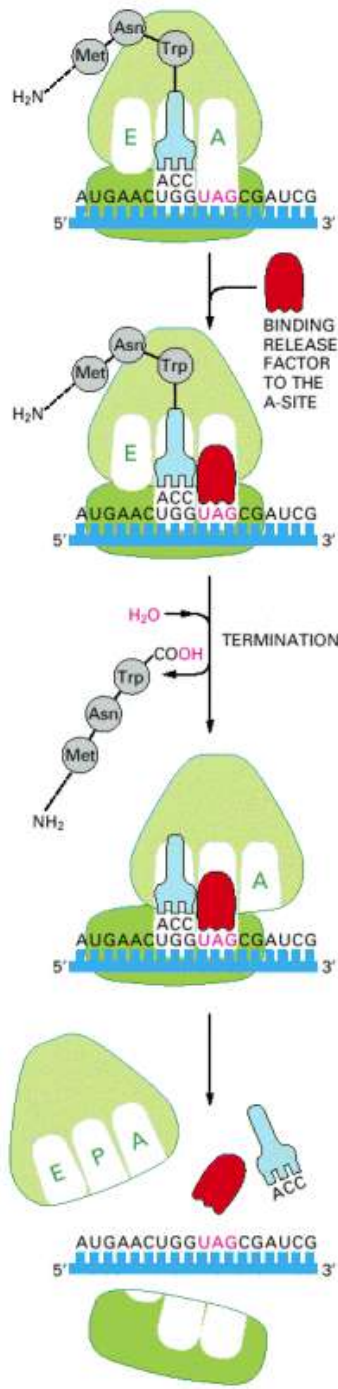

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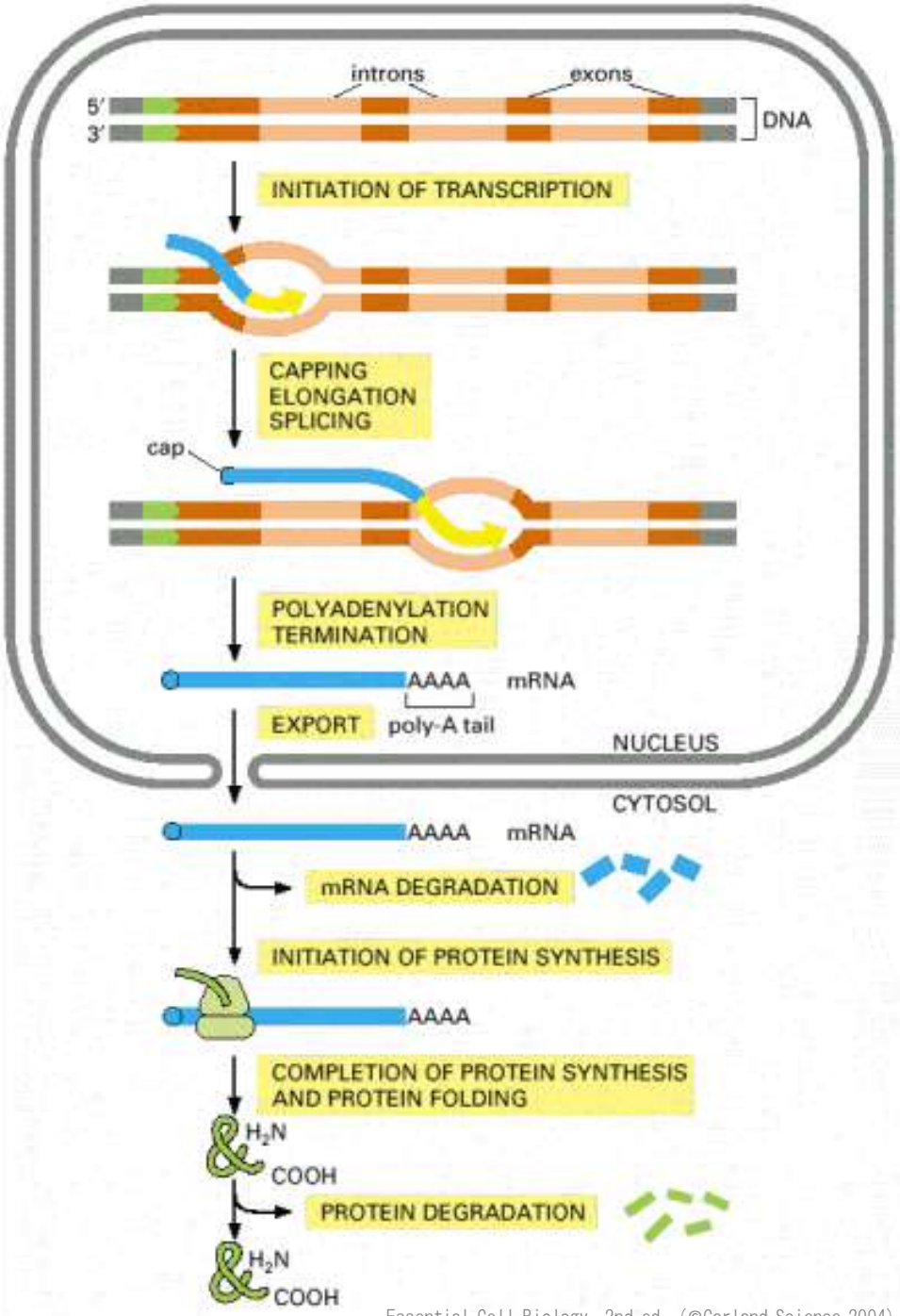

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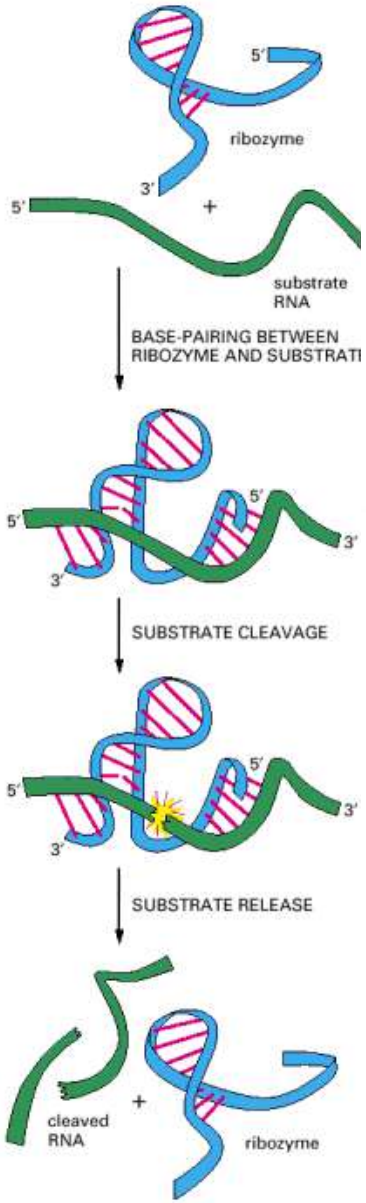
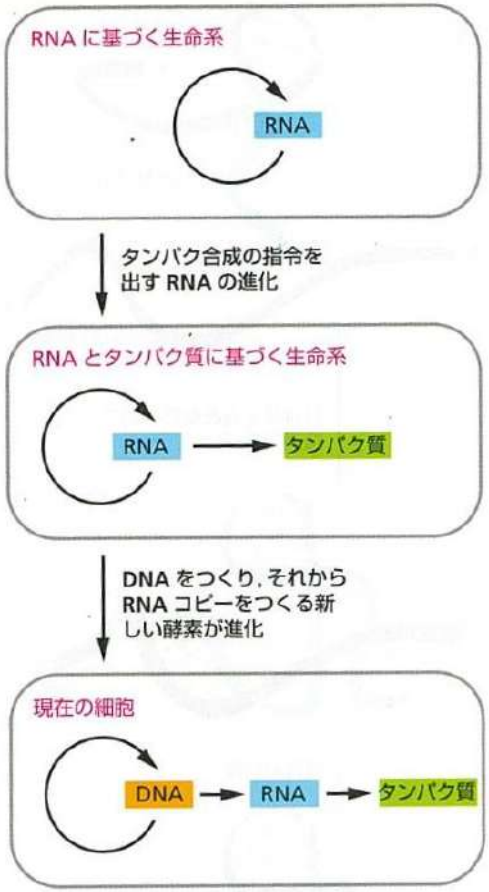


Essential Cell Biology, 1st ed. (©Garland Science 1998) 238p.



Bruce Alberts, Dennis Bray, Karen Hopkin, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter (2014). *Essential cell biology.* Garland Science.
(中村佳子・松原謙一(訳) (2016). Essential細胞生物学 南江堂) pp.256 図7-48

- RNA World
- Ribozyme リボザイム

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

https://www.gettyimages.com/photos/lou-gehrig

AP Photo/Findley Kember

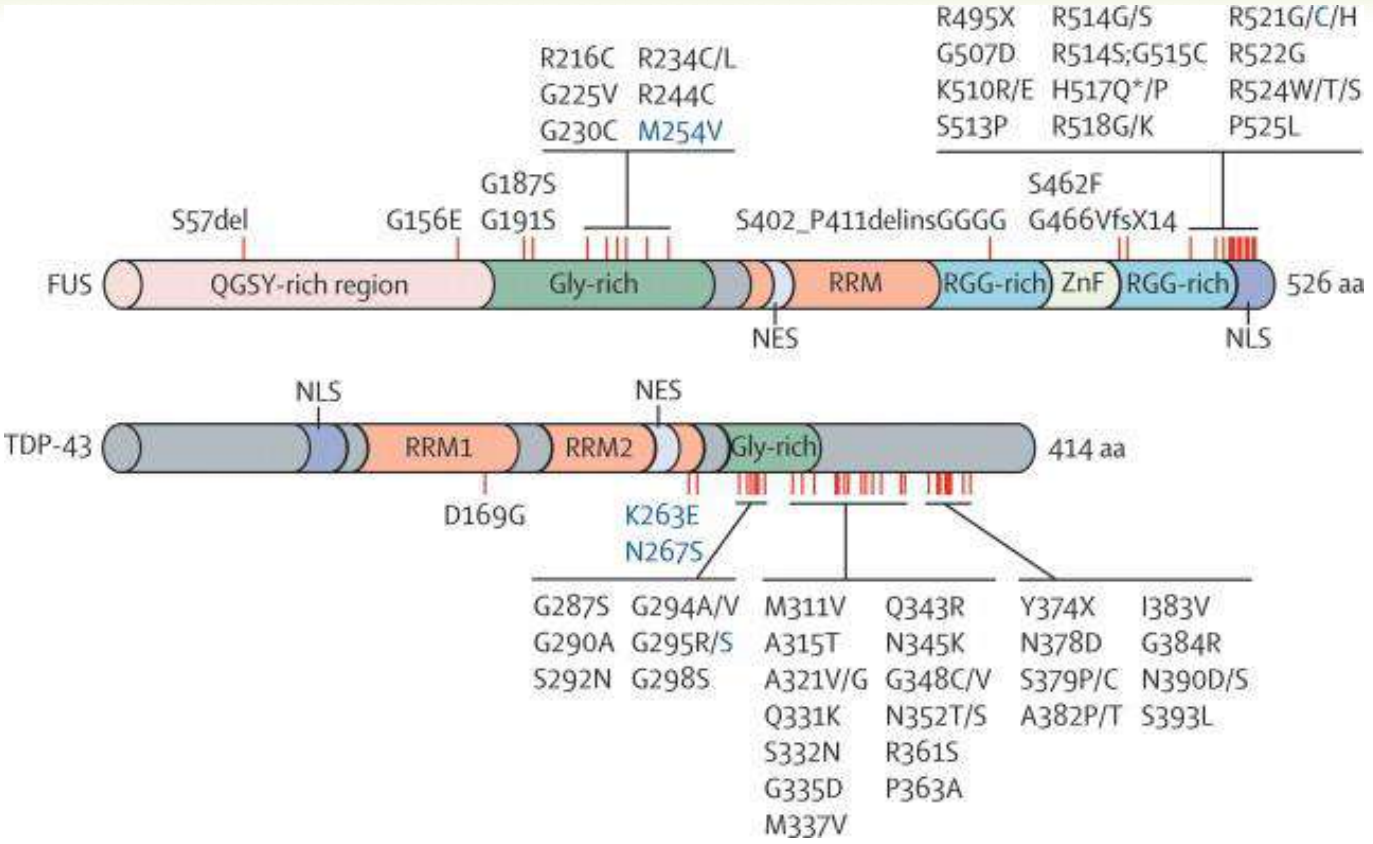
With the aid of an assistive device, such as a "sip-and-puff" switch, individuals can control motorized wheelchairs, communication devices, and computer programs.

- **Amyotrophic lateral sclerosis** (**ALS**), also known as Lou Gehrig disease, involves progressive loss of **motor neurons** (a type of nerve cell controlling muscle movements) in the brain and spinal cord.

- ALS is a progressive, disabling, and ultimately fatal disease of unknown cause. Walking, speaking, swallowing, breathing, and other basic functions become impaired with time. About 30 000 Americans currently have ALS. The yearly incidence rate is 1 to 2 new cases per 100 000 individuals. The disease is commonly discovered during middle age and affects more men than women.

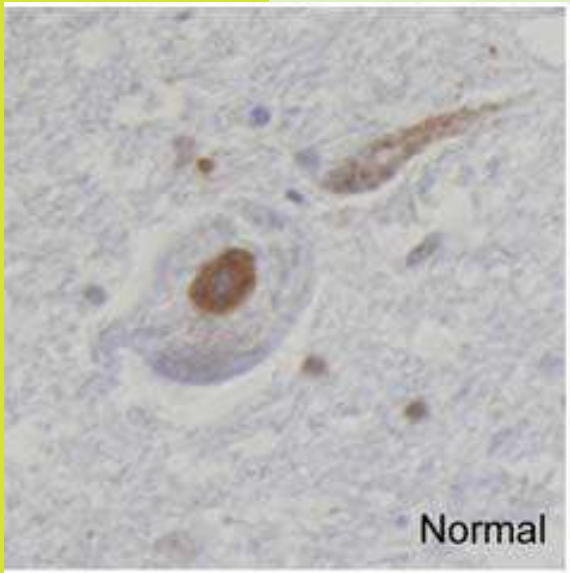
(JAMA Vol. 298 No. 2, July 11, 2007)

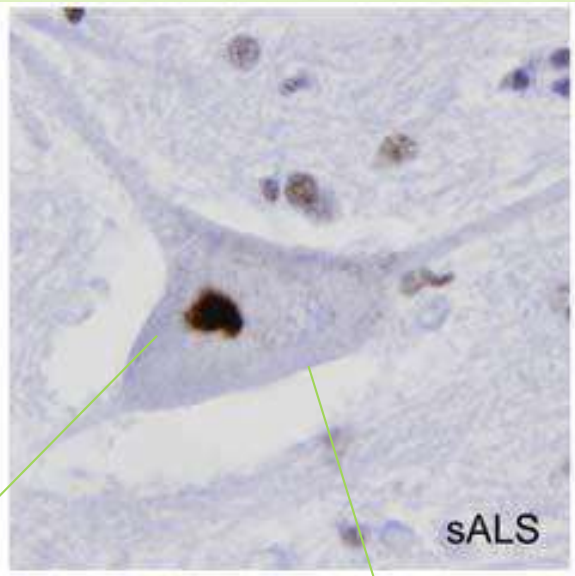
GENE MUTATIONS ASSOCIATED WITH ALS AND FTLD

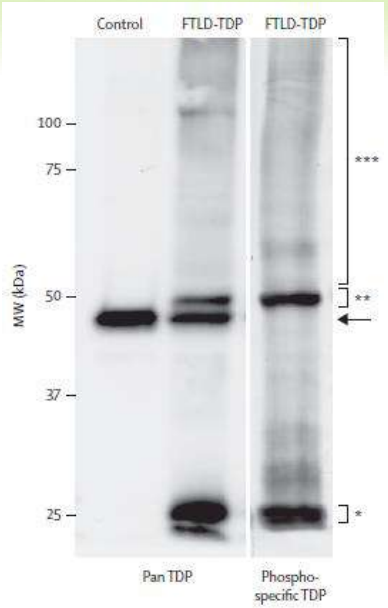


(The Lancet Neurologty Vol. 9, October 2010)

IMMUNOSTAINING OF TDP-43 IN SPINAL CORD MOTOR NEURONS





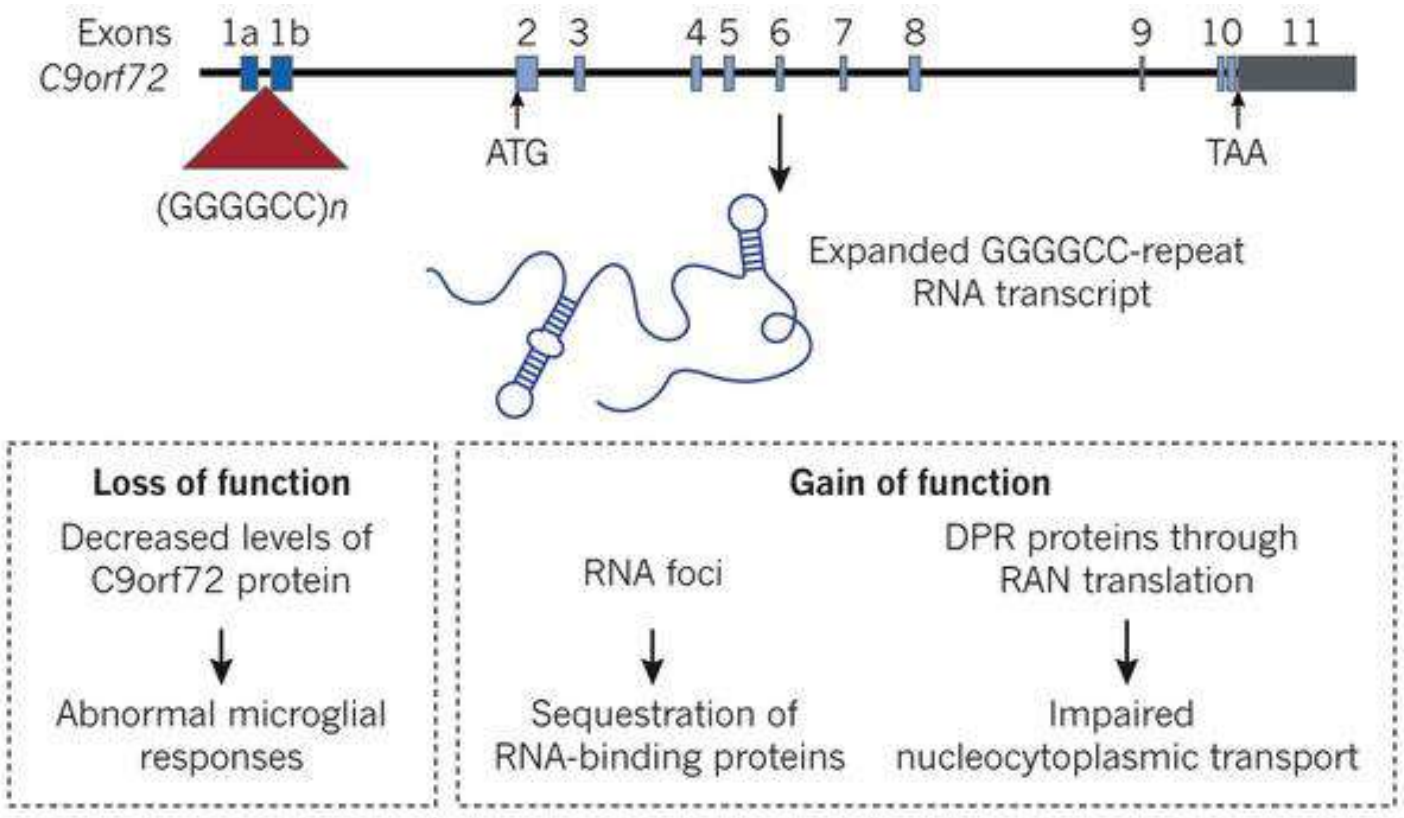


Cytoplasmic inclusions of phosphorylated C-terminal fragments of TDP-43

Absence of TDP-43 in the nucleus

Human Molecular Genetics, 2009, Vol. 18, Review Issue 2 R156–R162
The Lancet Neurologty Vol. 9, October 2010

C9ORF72-RELATED ALS

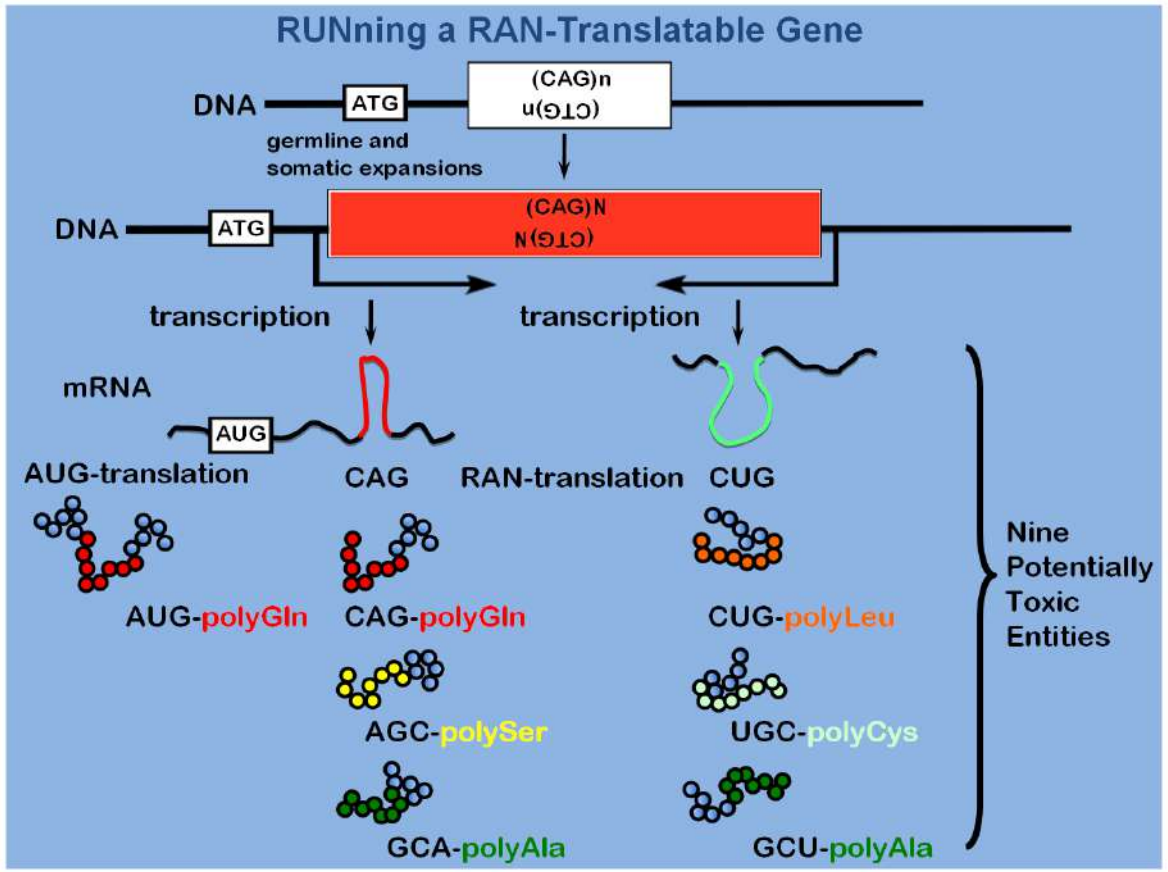


Nature **539**, 197–206 (10 November 2016)

ハンチントン病

- **1.「ハンチントン病」**常染色体優性遺伝型式を示す遺伝性の神経変性疾患。舞踏運動などの不随意運動、精神症状、行動異常、認知障害などを臨床像の特徴とします。これらの症状はいつのまにか始まり、ゆっくり進行します。

- **2.** わが国の調査では人口10万人あたり0.7人と欧米の1／10です。30歳くらいで発病される患者さんが多いのですが、小児期から老齢まで様々です。



http://www.nanbyou.or.jp/entry/175

PLoS Genet. 2011 Mar;7(3):e1002018.