Translation is that which transforms everything so that nothing changes.
—GÜNTER GRASS
retroviruses

Virus | RNA/DNA | Process
--- | --- | ---
Retroviruses | + RNA | - DNA
Poliovirus | + RNA | - RNA
Influenza Virus | - RNA | + mRNA
Reovirus | - RNA | + mRNA
Hepatitis B Virus | ± DNA | + DNA
Most eukaryotic mRNAs except organelle mRNAs and certain viral mRNAs

- 5'-7-methylguanosine (m7G) joined to second nucleotide of mRNA by 5'-5' phosphodiester linkage

- Directs pre-mRNAs to processing and transport pathways, regulates mRNA turnover, required for efficient translation by 5'-end dependent mechanism
5’-untranslated region

- 3 – >1,000 nt in length, typically 50 – 70 nt
- Often contains RNA secondary structures; must be unwound to allow passage of ribosome
- Length and secondary structure influence translation efficiency

3’-untranslated region

- Can regulate translation initiation, translation efficiency, mRNA stability
- poly(A) tail, necessary for efficient translation
Translational machinery

- Initiation proteins (eIF)
- Elongation proteins (eEF)
- Termination proteins (eRF)
5'-end dependent initiation
5'-end dependent initiation

5'-end-dependent initiation
Juxtaposition of mRNA ends

Pea enation mosaic virus
Barley yellow dwarf virus
48S initiation complex

Scanning

ATP → ADP + P_i

Hydrolysis of GTP in ternary complex

Joining

60S subunit
Which statement about the 5’-cap on mRNA is incorrect?

A. It consists of m7G joined to second nucleotide of mRNA by an unusual 5’-5’ phosphodiester linkage
B. It is present on most cellular mRNAs
C. It is required for efficient translation by 5’-end dependent initiation
D. It binds the cap-binding protein eIF4E
E. It is found on mRNA but not pre-mRNA
Other mechanisms for decoding have been discovered in virus-infected cells
Ribosome shunting

-80 kcal/mole
Ribosome shunting

- 35s mRNAs of plant caulimoviruses
- Late adenovirus mRNAs
- P/C mRNA of Sendai virus

Shunting is predicted to decrease dependence of mRNAs for eIF4F during initiation by reducing the need for mRNA unwinding.
Internal initiation

Viral (+) strand genome

Translation, processing

Capsid

Proteases and RNA synthesis

P1

P2

P3

VP0

VP3

VP1

2A

2B

2C

P3

VP4

VP2

3AB

3CDpro

3AB

3CDpro

3Dpol

A

A

3'

UTR

UTR

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IRES = internal ribosome entry site
No IRES

AUG  UAA

No protein

IRES

AUG  UAA

Translation

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eIF4G footprint
all eIFs

all eIFs except eIF4E

eIF2, eIF3
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What do ribosome shunting and internal ribosome initiation have in common?

A. Cap recruitment of 40S subunit
B. Both involve RNA secondary structures
C. Ribosome scanning through the entire 5’-UTR
D. Both require cap-binding protein eIF4E
E. All of the above
Methionine-independent initiation

- Can assemble 80S ribosomes without any eIFs or Met-tRNAi
- RNA mimics tRNAi
Methionine-independent initiation

Turnip yellow mosaic virus

- Can assemble 80S ribosomes without any eIFs or Met-tRNAi
- RNA mimics tRNAi
Maximizing coding capacity of the viral genome

- Polyprotein (Picornaviridae, Flaviviridae, Togaviridae, Arenaviridae, Bunyaviridae, Retroviridae)
- Subgenomic mRNAs (Rhabdoviridae, Paramyxoviridae, Togaviridae)
- Segmented genome (Orthomyxoviridae, Reoviridae)
- RNA Splicing (Orthomyxoviridae, Adenoviridae, Polyomaviridae)
- Internal initiation (IRES) (Picornaviridae, Flaviviridae)
- Leaky scanning (Retroviridae, Paramyxoviridae)
- Re-initiation of translation (Orthomyxoviridae, Herpesviridae)
- Suppression of termination (Retroviridae, Togaviridae)
- Ribosomal frameshifting (Retroviridae)
Polyprotein synthesis

A
Viral (+) strand genome

5' VPg
UTR

Translation/processing

P1
P2
P3

VP0 VP3 VP1 2A 2B 2C

VP4 VP2

2Apro 3Cpro

B
Viral (+) strand genome

5' C
UTR

Translation/processing

C prM E NS1 2A 2B NS3 4A 4B NS5

Host signal peptidase
Viral serine protease (NS3)
Leaky scanning

5' C

C proteins

AUG 104

P 568 aa

C' 215 aa

ACG 81

C 204 aa

AUG 114

Y1 181 aa

AUG 183

Y2 175 aa

AUG 201

A_nA_{OH}^{3'}
Suppression of termination

eRF1 and eRF3 recognize all 3 stop codons (UAA, UAG, UGA)

Stop codons may be recognized by charged tRNA - misreading, or charged suppressor tRNA (e.g. selenocysteine for UGA)
Suppression of termination

A

C
G
A
G-C
G-C
A-U
C-G
U-A
G-C
G-C

UAGGGAGGUCAG CAGGAUAACCCUCAAAGUCGGGGGG

5' C Gag Pol 3'

B

nsP1 nsP2 nsP3 nsP4

nsP2 proteinase

P123

nsP2 proteinase

P123

Readthrough translation

Translation

5' C

Nonstructural ORF Structural ORF

A\textsubscript{\textsc{tr}}A_{OH}3'
Ribosomal frameshifting

mRNA

Gag

Pol

Protein

Gag

N C

Gag-Pol

N C
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Compared with a polycistronic mRNA, a monocistronic mRNA:

A. Does not require an AUG start codon
B. Does not bind the 40S ribosomal subunit
C. Has only one open reading frame
D. Is only found in viruses and bacteria
E. All of the above
Regulation of translation in virus-infected cells

- **Initiation**
- **Elongation**
- **Termination**
PKR and cellular antiviral response

- PKR induced and activated by virus infection
- Leads to inhibition of host translation, apoptosis
- Different viral mechanisms have evolved to inactivate the PKR pathway
Adenovirus VA RNA I prevents activation of PKR

VA RNA I → PKR inactive → no phosphorylation of eIF2α subunit → active protein synthesis

dsRNA → PKR inactive → eIF2α subunit phosphorylation → protein synthesis inhibited
Viral proteins and RNAs that counter inactivation of eIF2
PKR is an interferon-induced enzyme that is activated by _____, leading to phosphorylation of _______ and inhibition of translation.

A. GDP, eIF2alpha
B. dsRNA, eIF2alpha
C. dsRNA, eIF2B
D. ssRNA, eIF2alpha
E. None of the above
Stress granules

Stress granules are cytoplasmic granules that form during cellular stress. They are composed of various RNA-binding proteins, including eIF4E, eIF4G, and eIF4A, and are implicated in the regulation of translation during stress conditions. Stress granules can form in response to various stimuli, including viral infection, nutrient deprivation, and oxidative stress. The formation of stress granules is thought to involve the sequestration of components of the eukaryotic translation initiation complex (eIF4F complex), preventing their use by the cell. The precise mechanisms that lead to the formation of stress granules are not fully understood, but they are thought to involve the activation of signaling pathways that promote the assembly of stress granules.
Viral inhibition of cell translation

A

Uninfected cells

Poliovirus-infected cells

Rate of protein synthesis

Time postinfection (h)

B

Time postinfection (h)

0 1 3 5 7

3CD

ICD

2BC

VP0

2C

VP3
Modulation of cap recognition

- elf4E dephosphorylation
  - Adenovirus
  - Influenza virus

Poliovirus 2A
Foot-and-mouth disease virus L

Cleavage

Dephosphorylation of 4E-bp1
Poliovirus
Encephalomyocarditis virus

5'-end-dependent initiation

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