بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | FINAL 20

# Regulation of Translation


**Written by :** DST
NST

**Reviewed by :** NST member

# وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا


**المعنى:** الذي وسع كل شيء رحمة وعلما، ووسع رزقه جميع خلقه، لا يحصي أحد ثناء عليه.

**الورود:** ورد في القرآن (٩) مرات.

**الشاهد:** ﴿إِنَّ ٱللَّهَ وَٰسِعٌ عَلِيمٌ﴾ [البقرة:١١٥].



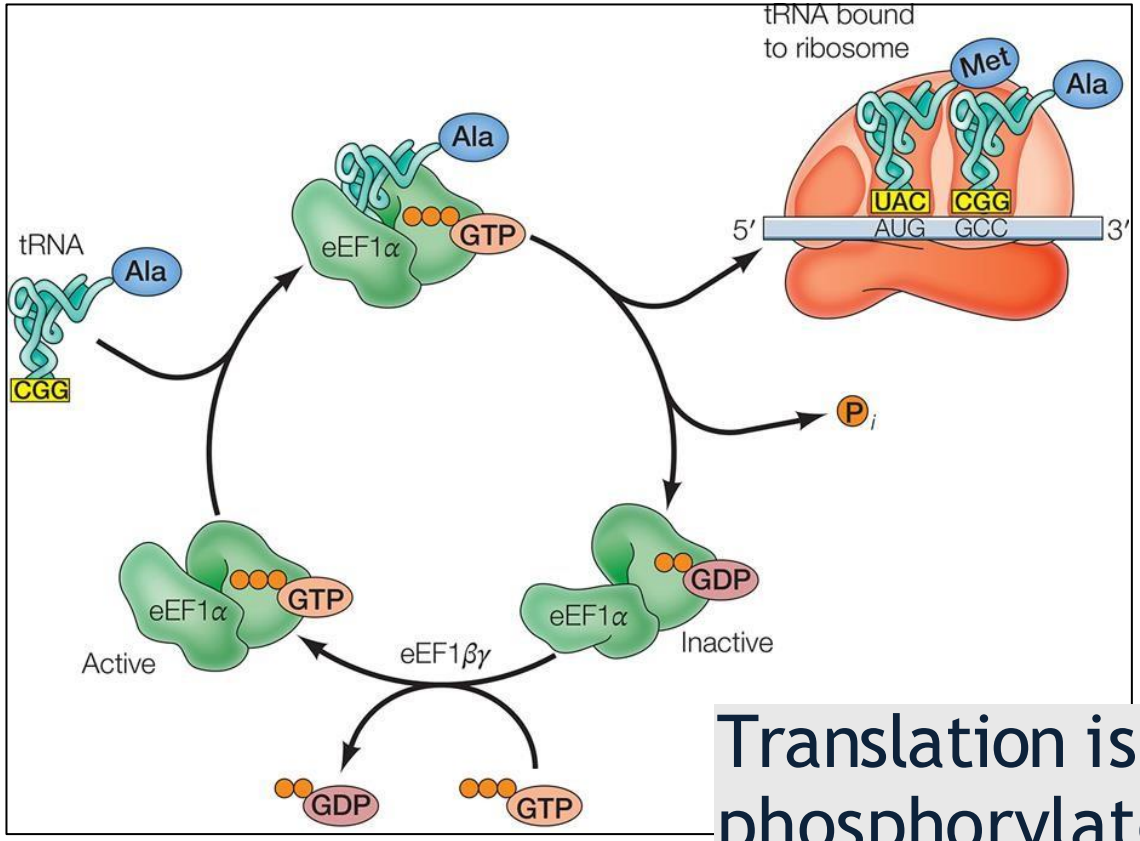
*اضغط هنا لشرحٍ أكثر تفصيلًا*

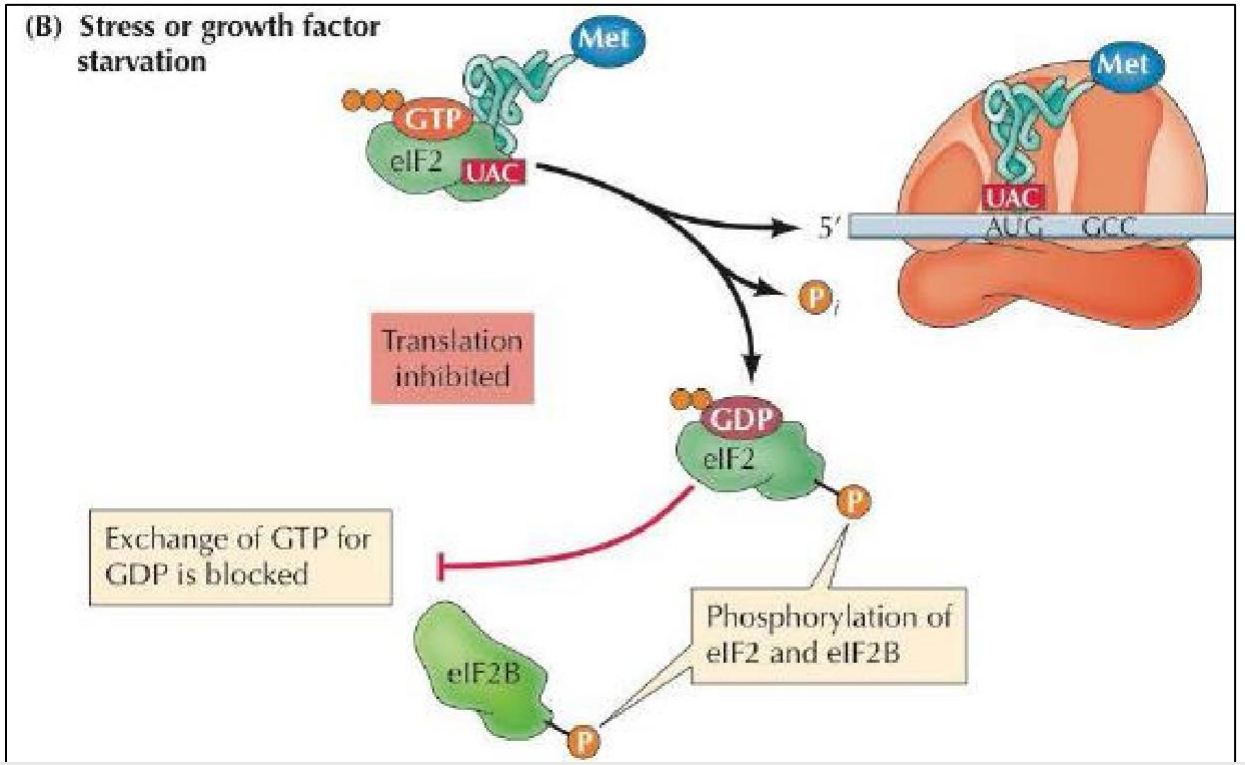
# Regulation of translation

- mRNA can be synthesized but may not be transcribed or get transcribed at a low efficiency/speed depending on the cell needs.

# Global regulation

- To continue translation, eIF2 must be reactivated by GTP/GDP exchange.

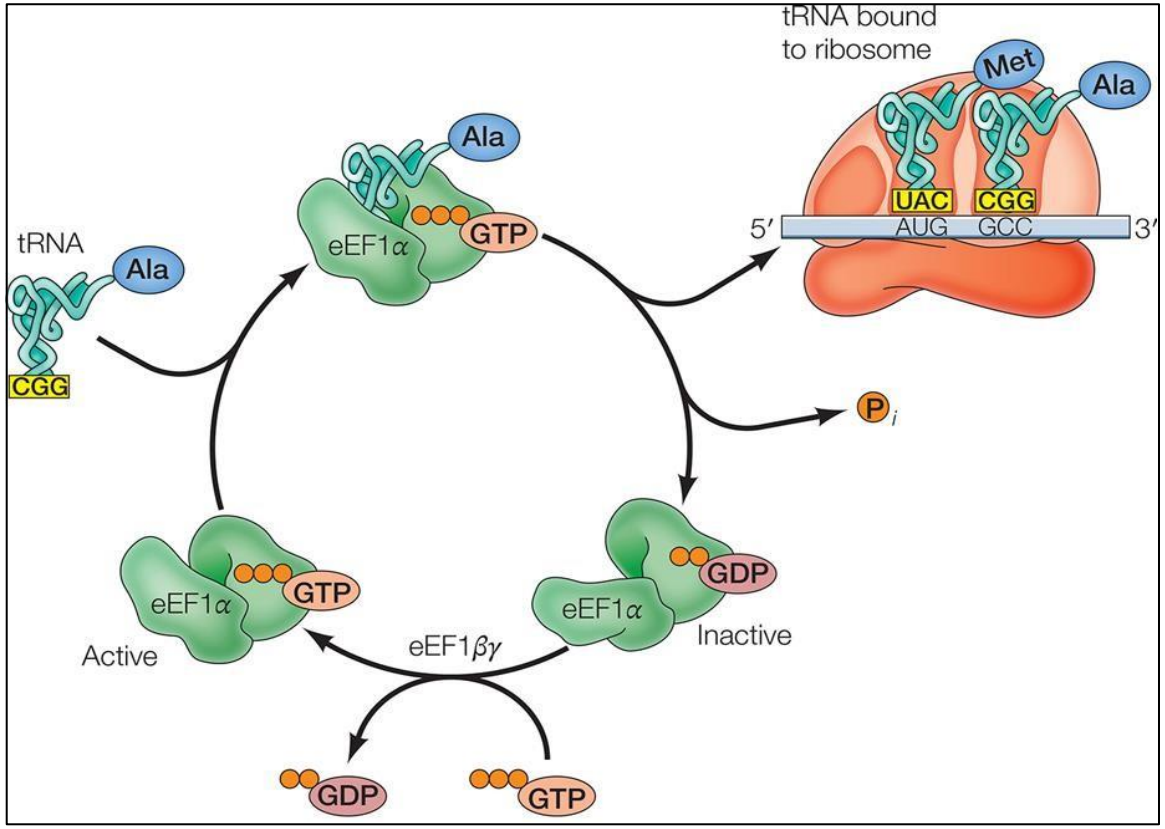



Translation is inhibited by regulatory kinases that phosphorylate eIF2 blocking the GTP/GDP exchange.

# Global regulation

- To continue translation, eIF2 must be reactivated by GTP/GDP exchange.




- The main function of eIF2 is that when bound to GTP, it brings the initiator tRNA(which recognizes the start codon and carries methionine) to the small ribosomal subunit & mRNA. After start codon recognition, **GTP is hydrolyzed to GDP**, allowing the large ribosomal subunit to bind to the small subunit.
- **The function of eIF2 depends on its binding to GTP.**
- In order to reuse the same tRNA, GDP must be exchanged to GTP and can bind to tRNA + "Met" complex.

- eIF1: brings next tRNA + amino acid complex to A chamber in ribosome.
- eIF4: brings mRNA to the tRNA + small ribosomal subunit complex (by binding to the 5' CAP and to the 3' poly-A tail via poly-A binding protein "PABP")

# Global regulation

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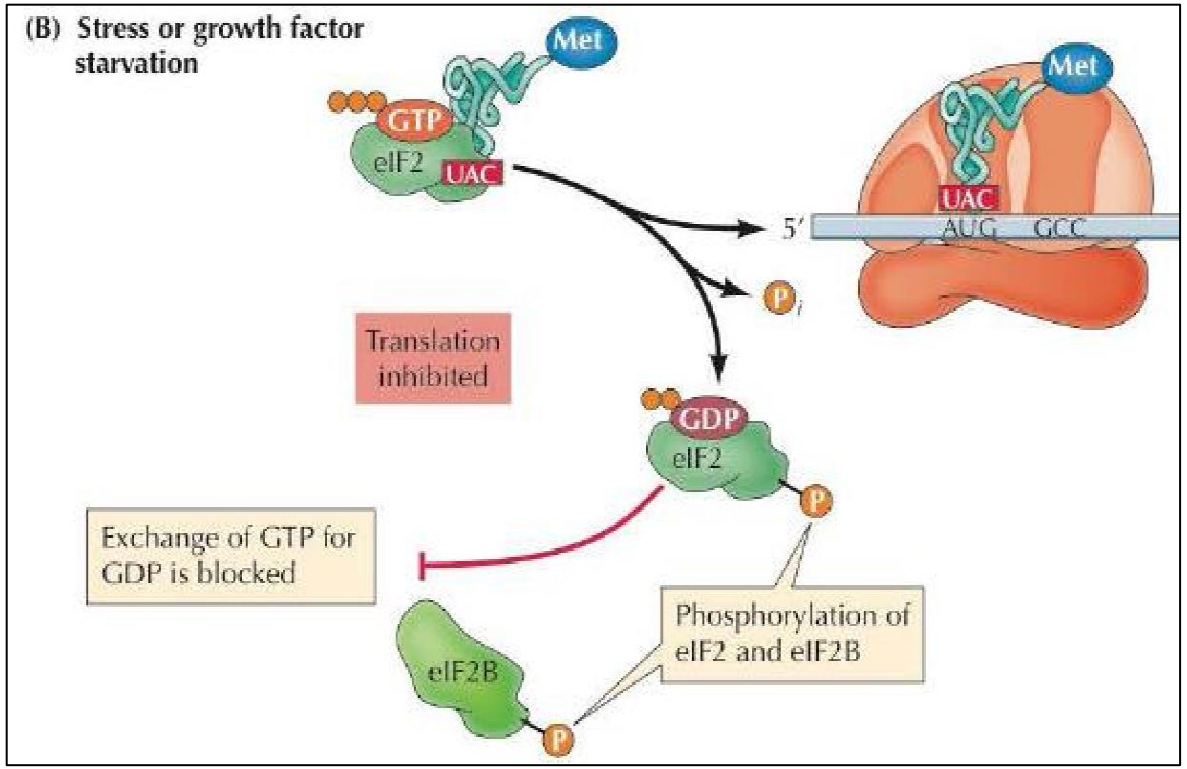



- When eIF2 is phosphorylated by a kinase, it <u>CANNOT</u> exchange GDP for GTP.

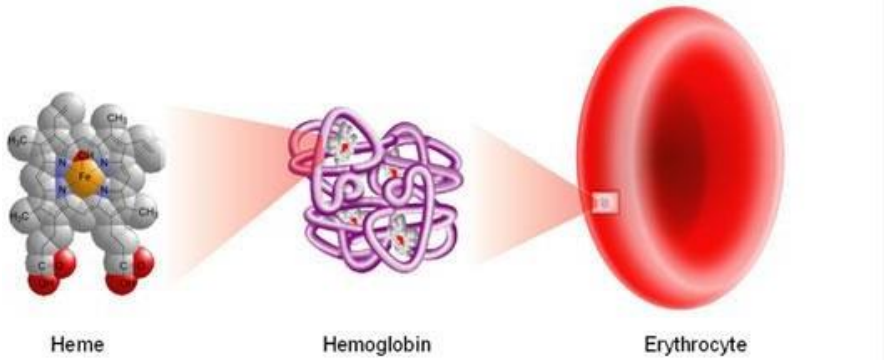
->inhibition of all translation processes .

This is exactly what happens to reticulocytes.

SEE NEXT SLIDE

# Heme and protein synthesis

- In reticulocytes (immature erythrocytes), if adequate heme is available, heme stimulates overall protein synthesis.
  - Reticulocytes undergo maturation to turn into Rbcs.
  - Rbcs MUST have a lot of Hemoglobin that carry O2.
  - The hemoglobin molecule consists of a heme group as well as a globin group, If the heme is insufficient, no globin molecules are synthesized.



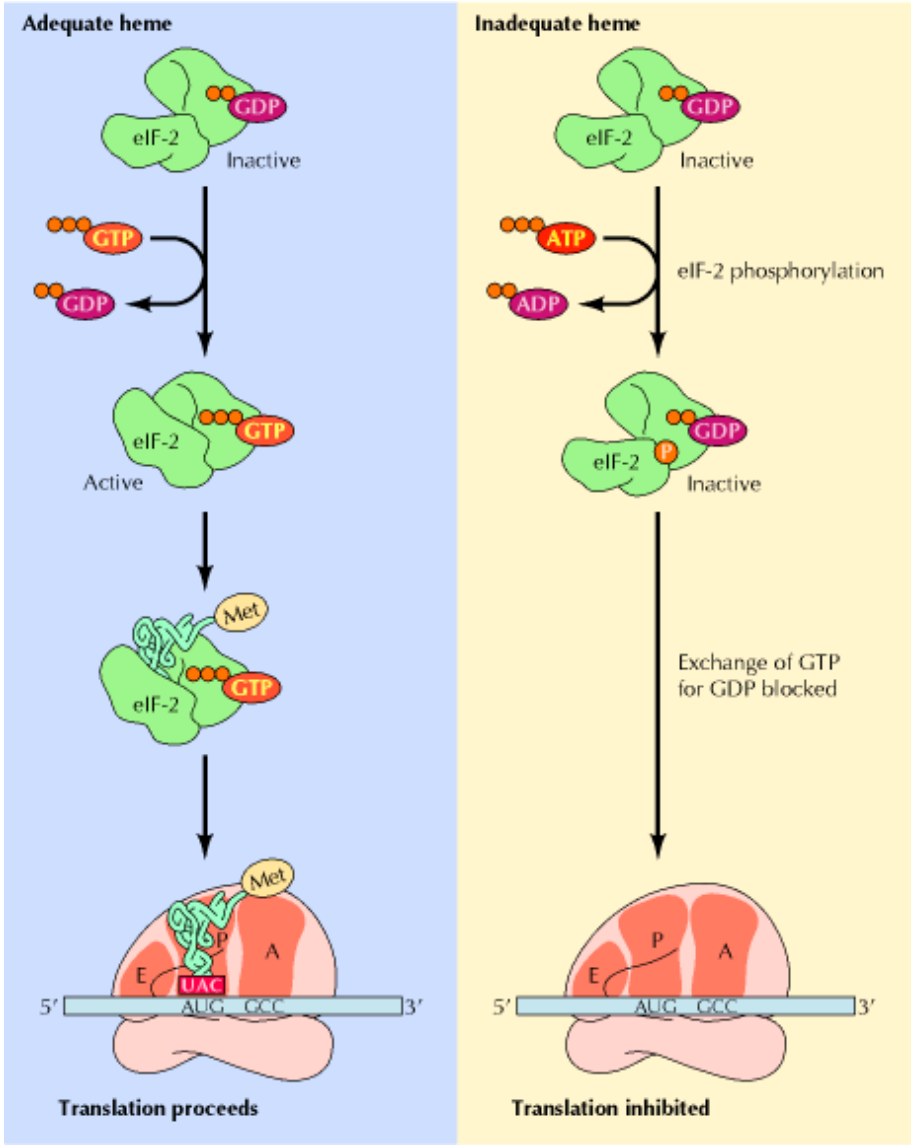
# Heme and protein synthesis

- If adequate heme is available, GDP-GTP exchange occurs and translation can proceed.

  eIF2 is active all the time.

- If heme supplies are inadequate, a protein kinase phosphorylates eIF2.

  No GTP/GDP exchange ->no translation occurs.

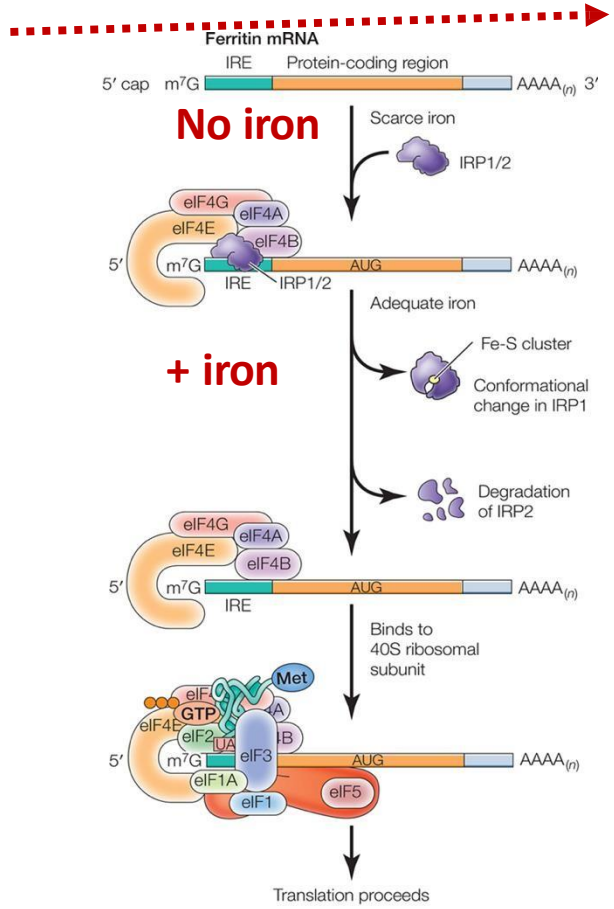


# Regulation of mRNA stability

- This regulatory mechanism is specific for mRNA And it deals with iron.

# Regulation of ferritin synthesis

- The mRNA contains an iron response element (IRE) near its 5′ cap.
- If iron is scarce, proteins called iron regulatory proteins 1 and 2 (IRP1/2) bind to the IRE, blocking translation by interfering with binding of the mRNA to the 40S ribosomal subunit.
- In the presence of iron, cells produce IRP1 is inhibited and IRP2 is degraded enabling translation of the mRNA.



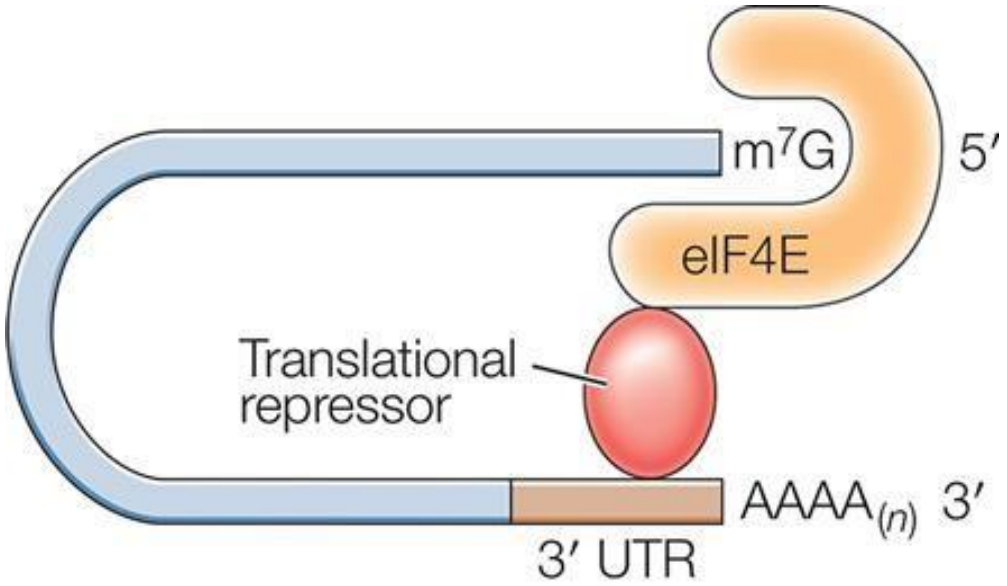

قالَ تعالى: (وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ)

# Regulation of ferritin synthesis

***Recall***:

- **In ferritin** > IREs located in the 5′ untranslated region (5′ UTR), upstream of the start codon (before AUG).
- **In transferrin receptor** > IREs located in the 3′ untranslated region (3′ UTR) of the mRNA, after the stop codon.
- The regulation of ferritin is the opposite of the regulation of transferrin receptor **(inverse regulatory relationship)**.
- **When iron level is low** >IRP binds to an IRE in the 5′ UTR, translation of ferritin does not occur ( vice versa for transferrin receptor).
- **When iron level is high** >iron binds to IRP , so translation of ferritin occurs ( vice versa for transferrin receptor).

# Regulation of eIF4E




- Translational repressors can bind to regulatory sequences in the 3′ untranslated region (UTR) and inhibit translation by binding to the initiation factor eIF4E, bound to the 5′ cap.
- This interferes with translation by blocking the formation of a normal initiation complex

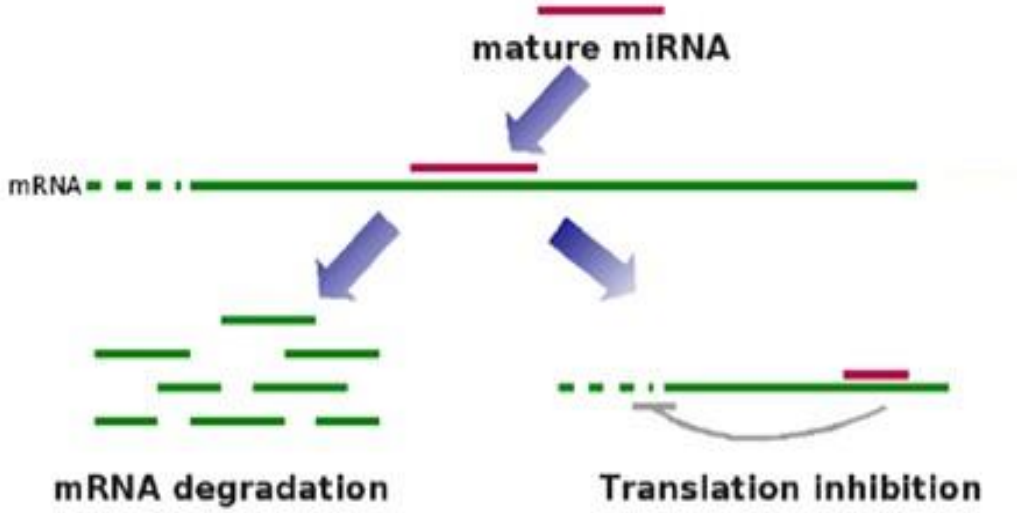
# Regulation by microRNA (miRNA)
## *and siRNA*

- Human cells make microRNA, about 4000 molecule in each, and that's a lot!!.

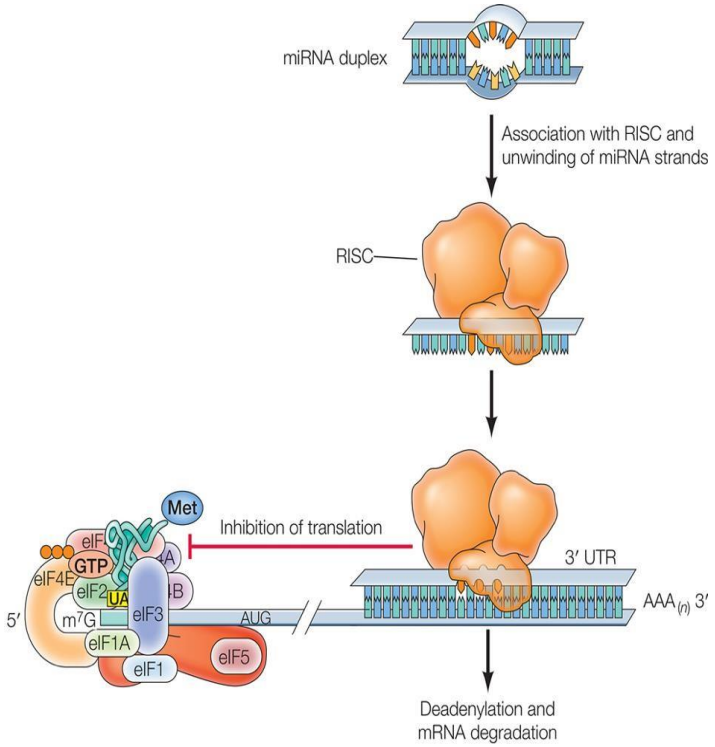
# Regulation by microRNA (miRNA)

- MicroRNA is synthesized by RNA polymerase II into single-stranded, primary miRNA (pri-miRNA) transcript.

- It (miRNA) gets processed into double-stranded molecules but only one strand is loaded onto the RNA-induced silencing complex (RISC), a complex where miRNA targets and binds to the 3'-UTR of mRNA.
- The end-result is:



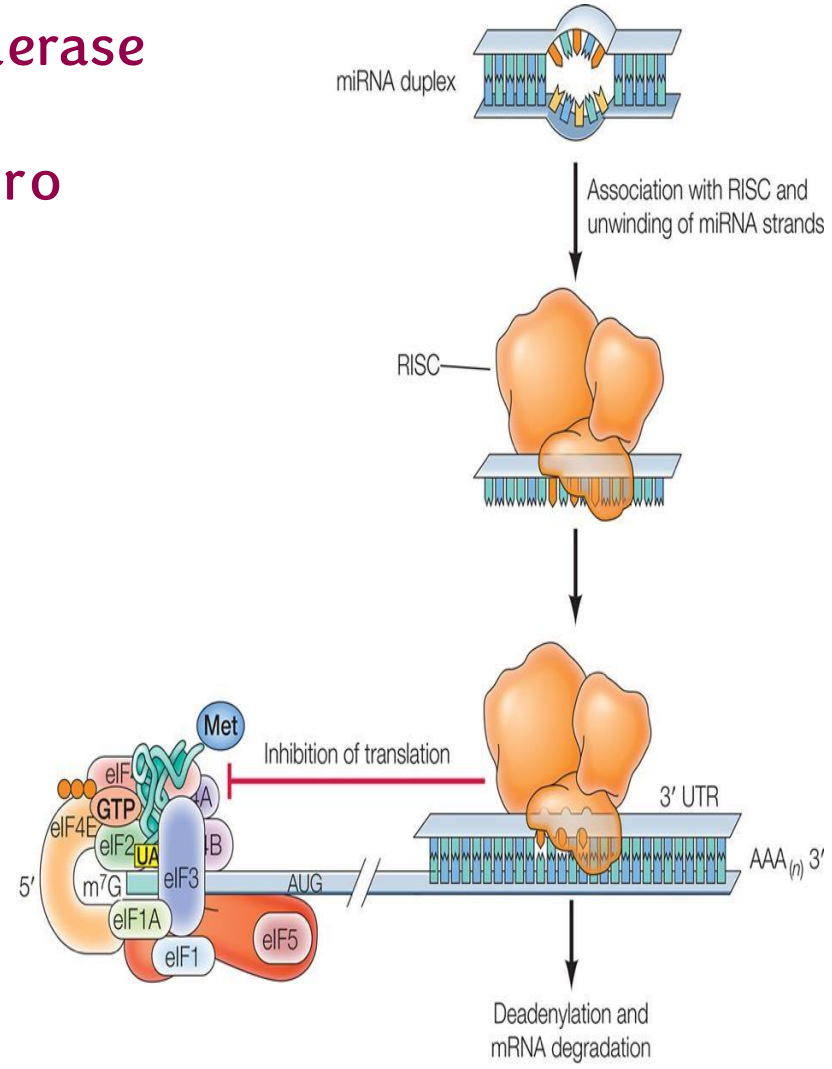

Further explanation Next slid



# Regulation by microRNA (miRNA)

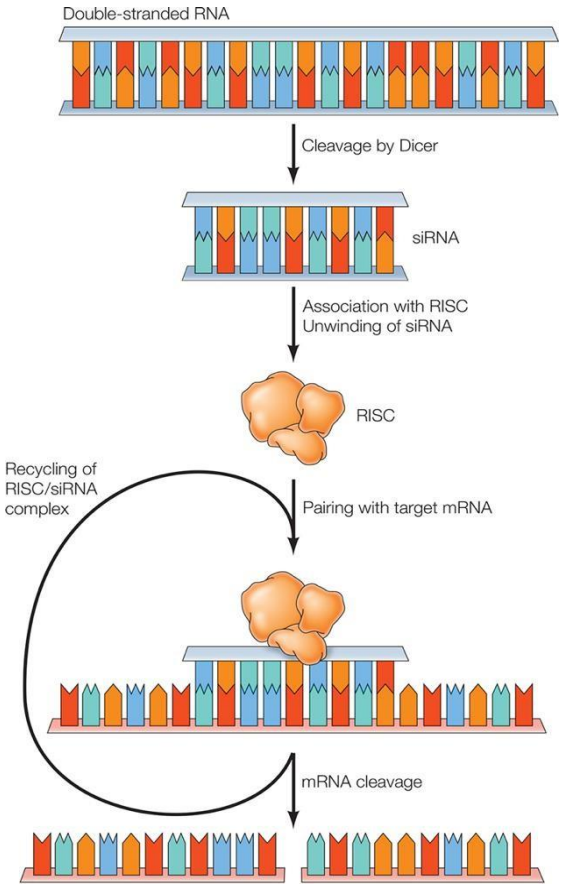
- miRNA is synthesized by RNA polymerase II, the same polymerase that makes mRNA. And it's a **short RNA molecule** (about 20 nucleotides), that's why it's called miRNA, because it's micro compared to mRNA that contains hundreds or thousands nucleotides.

- miRNA molecules are synthesized as **double-stranded RNA**. A protein called **RISC** ( RNA induced silencing complex) binds to **one of miRNA strands,** and transport it to **hybridize** to a sequence in 3' UTR (that is complementary to micro RNA) on mRNA molecules.
- Binding of miRNA to mRNA causes either **degradation of mRNA or inhibition of translation**. And, hence, **protein level decreases.**
- So, miRNA has a negative effect on protein levels.



# RNA interference and short interfering RNA (siRNA)

- Targeting mRNA by synthetic siRNA (short interfering RNA) can be used for experimental and therapeutic purposes.
- The double-stranded siRNA associates with the RISC complex, which targets one strand onto a homologous mRNA.
- The mRNA is cleaved and, as a result, the protein level decreases or the protein is not expressed at all.

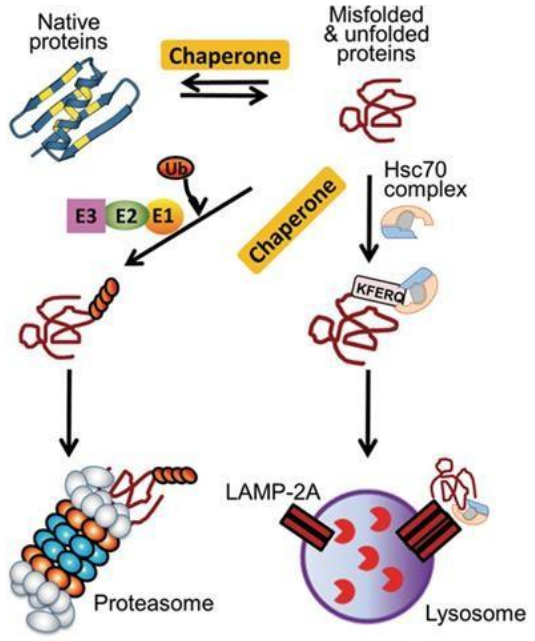



- siRNA works by the same mechanism of miRNA, but it's synthetic, that's, it's not normally synthesized in our cells, and we've taken advantage of it in therapy.
- Treatment nowadays is either immunotherapy, monoclonal antibody (against important proteins to cells) or siRNA (by blocking the production of certain proteins).

# What else?

# Fate of (mis)- and (un)-folded proteins

- Proteins are degraded either in degradative subcellular organelles like lysosomes or by the macromolecular proteasomes when they are uniquitinylated.
  - ***Recall***: If proteins are not folded properly, the cell first tries to refold them. If these attempts fail, small peptides called ubiquitins are attached to the protein in a process called ubiquitination in the cytosol, and then the protein is delivered to the proteasome (بعمل زي الجاروشة) for degradation.




  - Protein level is maintained by regulating transcription, translation and degradation of proteins such as mis-folded and un-folded proteins.

# The multi-levels of regulation

# Levels of regulation

Prof. mentioned the highlights of these mechanisms that we've already studied, check out the lecture.

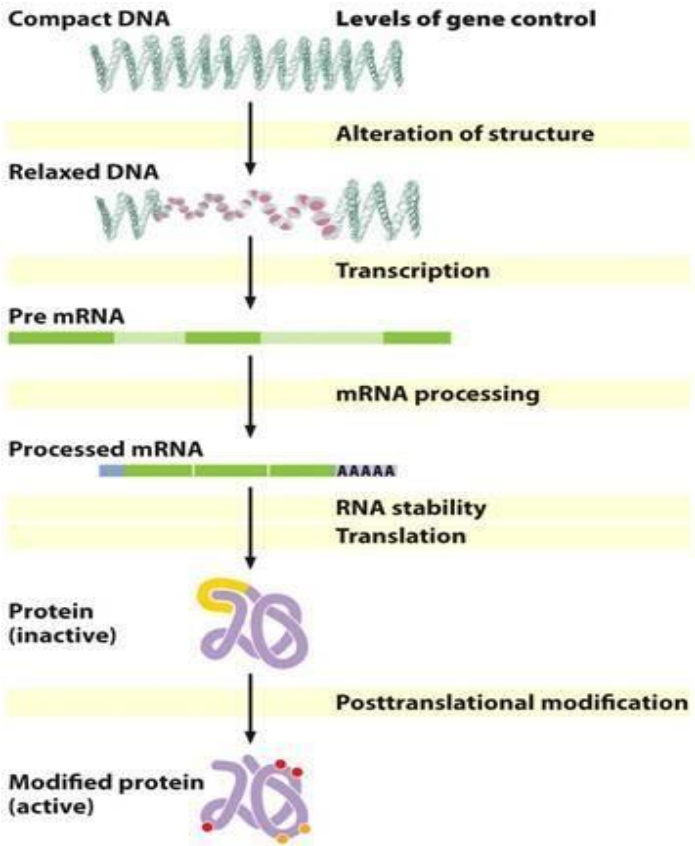



Figure 16.1
*Genetics: A Conceptual Approach*, Fifth Edition
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- Transcription
- RNA processing
- RNA transport
- mRNA stability
- Translation
- Post-translational modification
- Protein activity
- Protein degradation

- Regulation at different levels makes human cells different than animal cells. This what makes human human and mouse mouse. It's not always about on and off, it's about regulation.



دعواتُكم الصادقة لنا...

# رسالة من الفريق العلمي:

قال كعب بن زُهير:

لو كنتُ أعجبَ من شيءٍ لأعجبني ... سعيُ الفتى وهو مخبوءٌ له القدرُ
يسعى الفتى لأمورٍ ليس يُدركها ... والمرءُ ما عاشَ ممدودٌ له الأملُ
لا تنتهي العينُ حتى ينتهي الأثرُ ... والنفسُ واحدةٌ والهـمُّ منتشرُ

اسعَ في دروب الحياة ولا تنشغل بما قُدِّر لك، فإن الأقدار بيد الله وحده. خُذ بالأسباب كما أُمرت، ثم فوِّض أمرك إلى الله، مصداقًا لقوله تعالى:

﴿وَأَنْ لَيْسَ لِلْإِنْسَانِ إِلَّا مَا سَعَى﴾

واعلم أن السعي لا يضيع، وأن الرزق بيد الله، كما قال النبي ﷺ:

«لو أنكم تتوكلون على الله حق توكله لرزقكم كما يرزق الطير؛ تغدو خماصًا وتروح بطانًا»

# For any feedback, scan the code or click on it.

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | | | |
| V1 → V2 | | | |