Genetics & molecular biology

◉ Sheet ○ Slide

Number: - 15

Done by: - Mai Faisal & Hamdi Dabbas

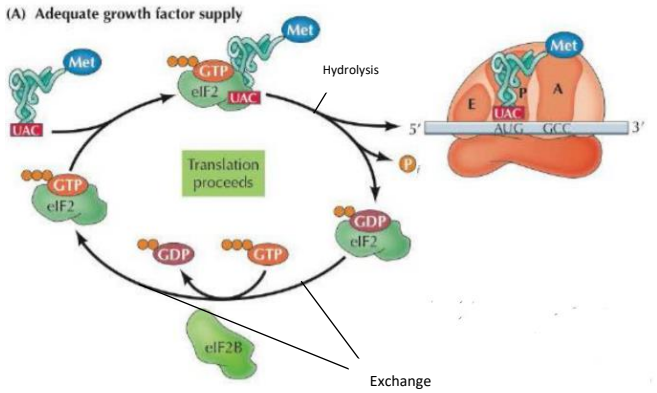
Corrected by: - Omar Bassam

Doctor: - Mamoun Ahram

Regulation of translation:

In this lecture we will be talking about regulation of translation which can be regulated globally, meaning that all processes of translation will be either activated or shut down, this happens when a cell has either adequate or inadequate growth factors or nutrients.

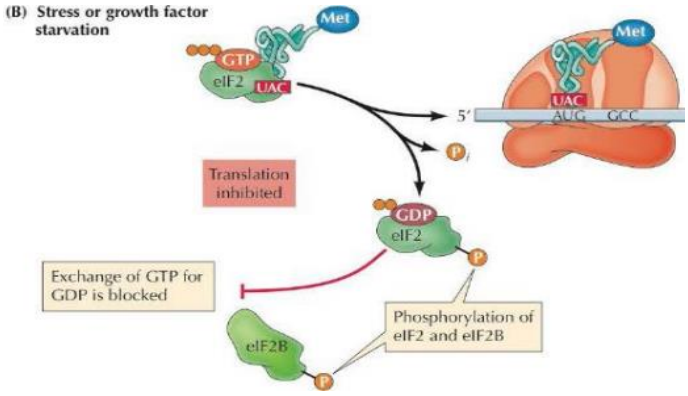
adequate growth factors



So, when the cell has inadequate nutrients, it needs to maintain the energy left and not consume it in synthesising proteins that might not be necessary for the cell's survival, so the cell stops the translation all together until we have available nutrients.

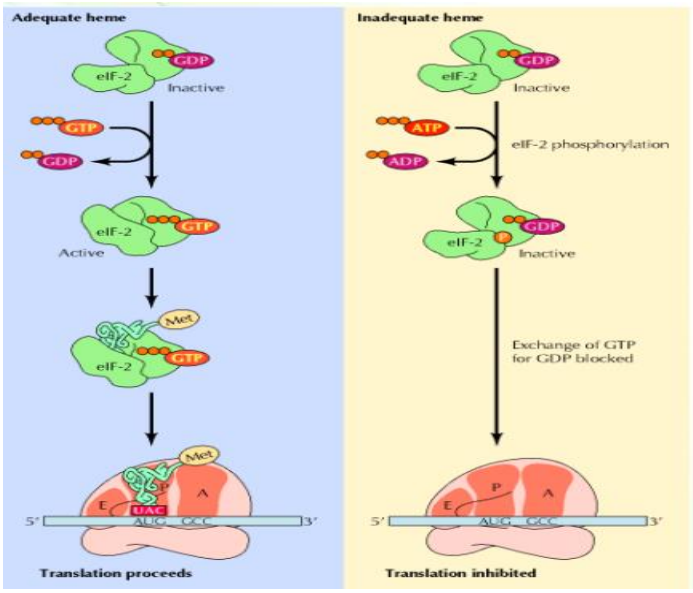
Recall from the previous lecture We talked about initiation factor (factor 1,2 and 3) we will focus on initiation factor 2 (IF2) which becomes active when it binds GTP, when it's active it binds to tRNA (initiating tRNA) which carries Methionine, and it takes it to the ribosome.
When initiation factor 2 binds GTP and completes its action, it hydrolyzes GTP to GDP rendering itself inactive, therefore it needs to bind to GTP to get reactivated, so we have another mechanism which is exchange meaning that GDP will be released and GTP will bind now to initiation factor 2, so it can bind to another tRNA …etc

We have another mechanism of regulation for initiation factor 2 activity which is phosphorylation of the IF2 protein itself; when it's phosphorylated it becomes inactive because it's bound to GDP and the GDP cannot be released from the protein, in conclusion, when we have inadequate growth factors/nutrients the kinase becomes active and phosphorylates the initiation factor 2 which will stop translation all together (because regulation is global)

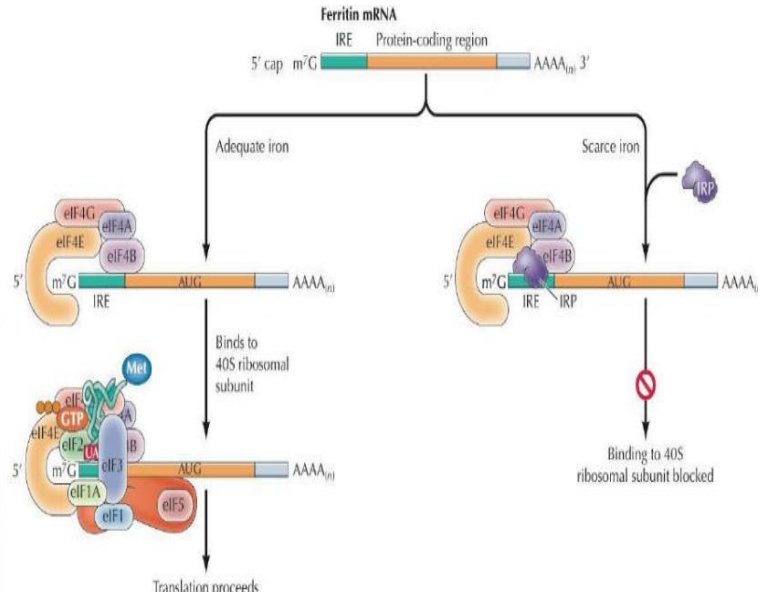


Note (not included): Prokaryotes have only 3 Initiation Factors: IF1,2 and 3. Whereas Eukaryotes have more Initiation Factors such as eIF1,2,3,4,5 and 6

Another example of hydrolysis and exchange processes:
In reticulocytes (mature erythrocytes) which produce hemoglobin which requires heme & globin, the presence of heme regulates translation (globally), therefore, when we have adequate heme the exchange will happen and the initiation factor 2 can still work, but if we have inadequate heme the kinase will work which means GDP cannot be removed resulting in inactive initiation factor 2…etc



Now ferritin is regulated at the transitional level, when we don't have enough iron, the iron response element binding protein (IRP) binds to the 5' untranslated region of the ferritin mRNA which will block its translation, how? We said that capping and poly A tail are both important for translation since the looping that happens between the poly A tail and the proteins around the cap help in stabilizing the initiation complex, but when the IRP binds to the IRE the interaction between the cap and the poly-A tail won't occur resulting in the regulation of the ferritin protein. (check the previous lecture)



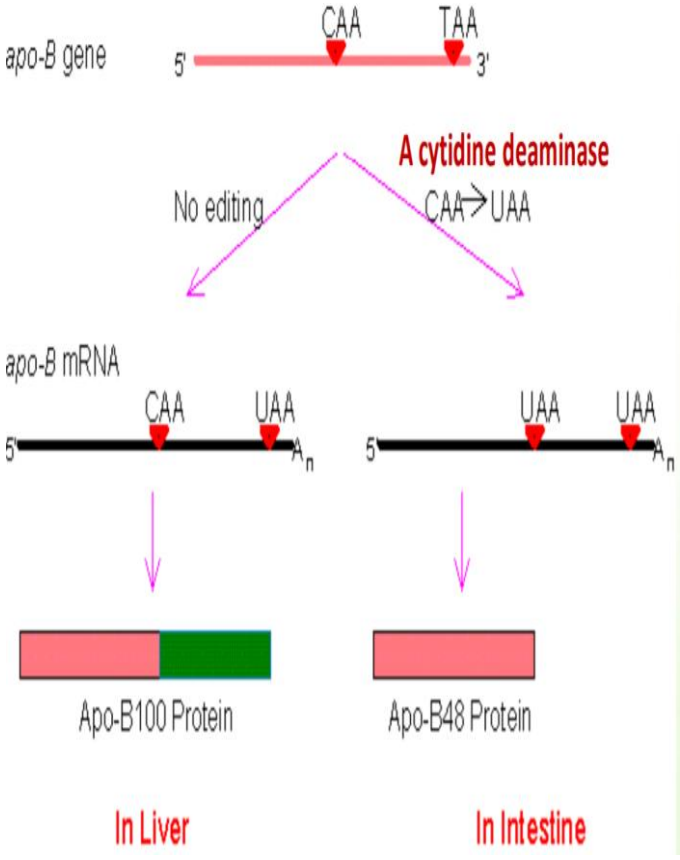
Gene editing as a mechanism of regulation:

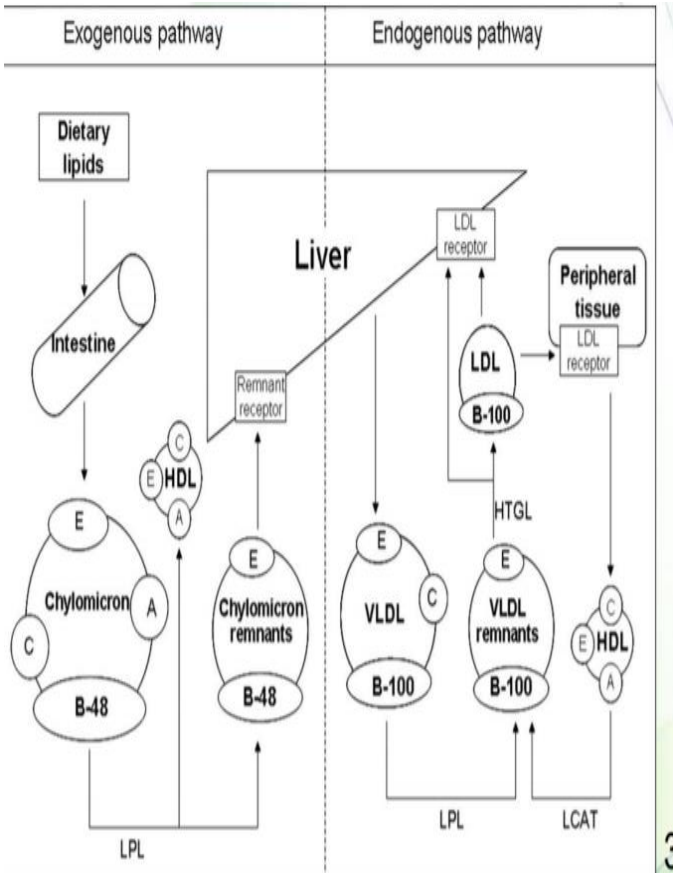
As we took in the biochemistry 2 courses, we have several lipoproteins to transport lipids between liver/intestines/peripheral tissues, Chylomicrons transport lipids from intestine to the liver and has the ApoB-48 protein, another lipoprotein is VLDL which transports lipids from the liver to the peripheral tissues, but it has the ApoB-100 protein, surprisingly both are synthesized from the same gene, this happens by **gene editing.**

The difference between B-100 and B-48 is in their molecular weight, B-100 is 100 kDa and B-48 is 48 kDa

This happens because the intestines have an enzyme called Cytidine deaminase, which deaminases Cytidine to become Uracil, this causes the mRNA to be edited in the intestines producing a stop codon -UAA- instead of the original -CAA- which results in a shorter polypeptide (check the pic below)

Important note: editing doesn't happen on the DNA strand; it occurs on the mRNA strand, <u>which means no mismatch repair can occur</u>.

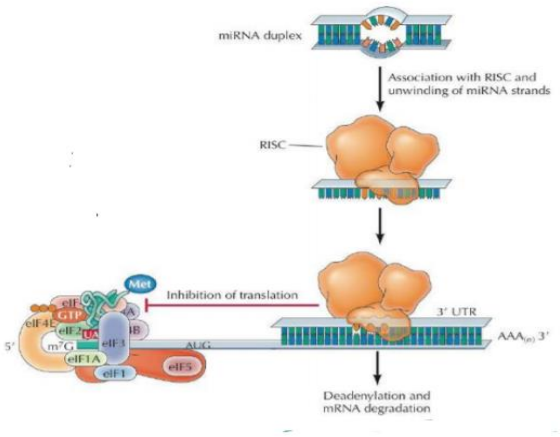




Micro RNA

We talked previously about how certain miRNA sequences can be complementary to sequences present on the 3’ untranslated regions (UTR) of certain mRNA, so binding happens between mRNA and miRNA which results in either degradation of mRNA or blocking of translation.

Where does miRNA come from? They can normally exist on the genome and have their own promoters making a non-coding RNA, or they can come from introns, in the end, RNA Pol II is responsible for synthesizing miRNA into single-stranded primary miRNA (pri-miRNA), which is then processed in the nucleus by Drosha and exported to the cytoplasm, then modified by endonuclease complex called Dicer forming a miRNA duplex.



After a miRNA duplex is formed(check the pic), a protein complex called RISC takes one of miRNA strands and guides it to a mRNA that has a complementary sequence to the miRNA and binds to the 3’ of the UTR blocking the translation because no interaction between poly A and the cap happens, and the mRNA would be degraded. Eventually, protein levels are reduced.

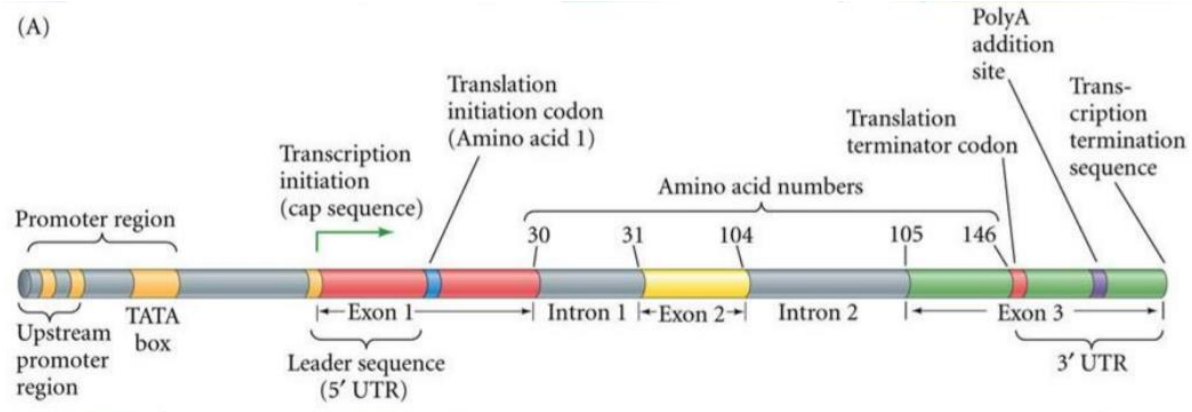
We also have talked about Alternative Polyadenylation, where cells would choose which poly A site to terminate transcription. Also, we talked about the effect of SNPs in the poly A sites. (the Dr. just mentioned these two points and moved on).

The mechanism of protein degradation (Fate of (mis)- and (un)-folded proteins)

One of these mechanisms is by tagging them; this happens by binding of small molecules called ubiquitin to proteins by a process known as ubiquitylation which marks the protein as destined to be degraded, these tagged proteins are taken into big barrel-shaped complexes called proteasomes where they end up degraded. (Recall Biochemistry 2)

Anatomy of a eukaryotic gene.

The Dr. just viewed the slide and went over the things we have discussed earlier on.



*Transcription must start from Exon 1

*Translation starts at a point that's downstream transcription start site (Exon1)

***Translation** terminator codon is **upstream** of the **Transcription** termination codon

Now when you end the molecular biology part of the course you should have studied all of the following subjects:

- Transcription (cis- and trans-acting elements)
- RNA processing (splicing)
- RNA transport (Actually, we didn't talk about this part in detail)
- mRNA stability (degradation; miRNA)
- Translation (ferritin)
- Post-translational modification (phosphorylation, etc.)
- Protein activity (inhibitors)
- Protein degradation (e.g. ubiquitination)

<u>If anything is not clear don't hesitate to ask any of us</u>

**As for the first 10 mins.
The doctor started with two stories this weekend
The first one is a murder case for a 12_year old girl that happened 40 years ago back then they couldn't know the criminal but now since we could do DNA analysis they compared it with the database they have, but no match was found, so they used a site called family tree DNA which is based on people's DNA analysis. The site tells people their origin and links them with their family in other countries. So the people who handled the case used the site and knew the killer.

The 2nd one
Is about a Chinese scientist which used crispr cas9 technology for gene editing and took a gene from the zygote ,the gene that was removed is a receptor that enters HIV to our cells, so they became immune from HIV, also that same receptor when removed the cognitive ability (intelligence) is increased, so the 2 babies were found to be smart. But still, there are other functions that we don't know for that receptor. so it's still considered an ethical problem

As for the exam the doctor recommended us to study in groups he also tends to connect information from different lectures he that he googles the questions but not necessarily the same questions, he may take only the picture from them so don't rely on them but it's good to take a look
You can also take a look at his past papers questions, but it's not necessary that he will write the same questions.

Good Luck