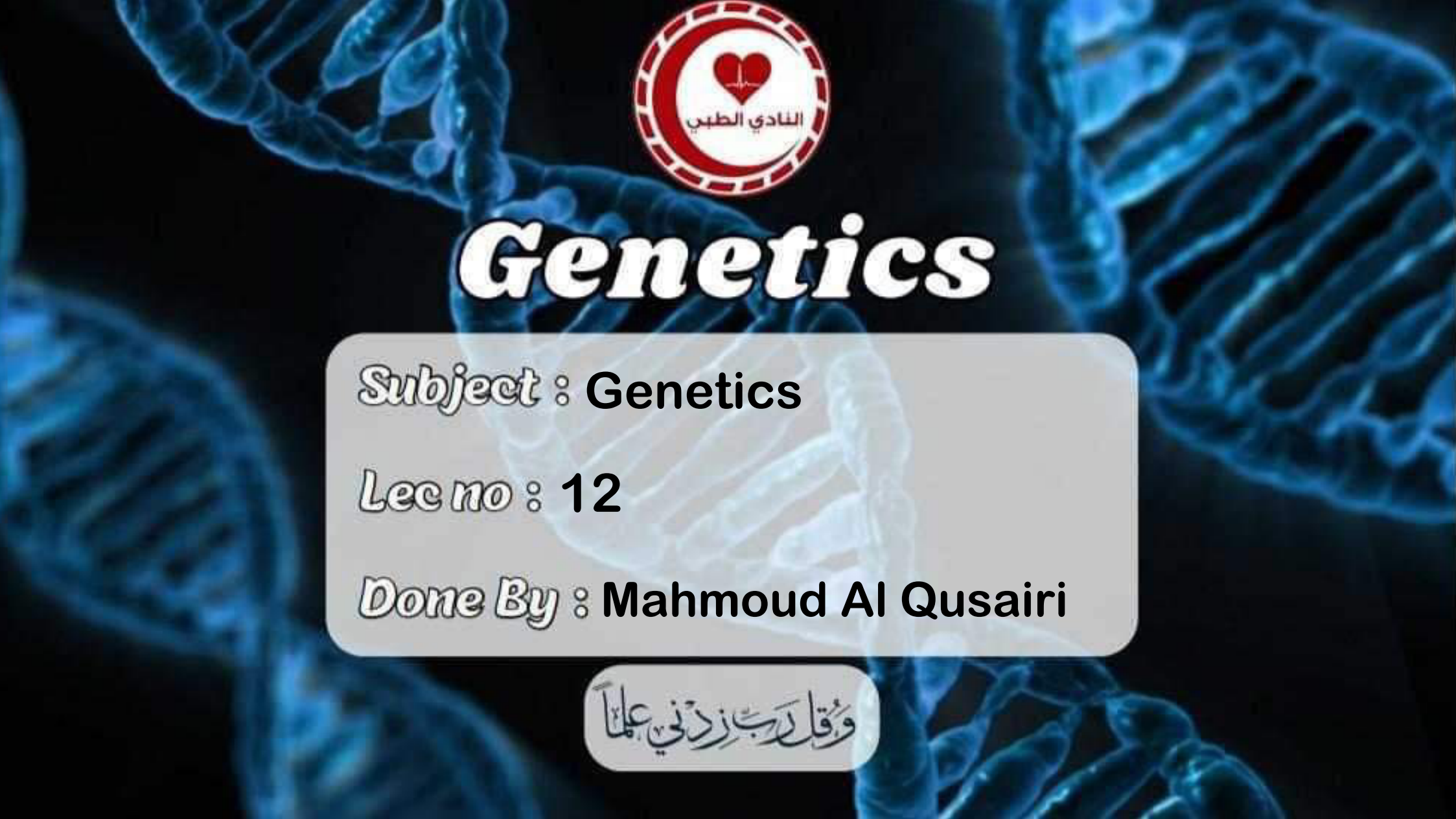
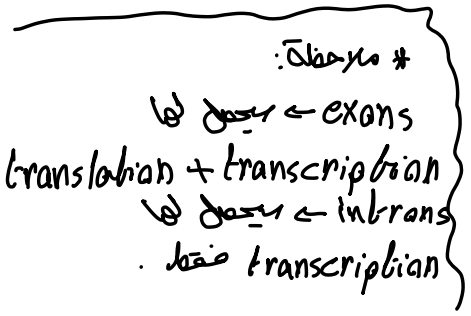

النادي الطبي
Genetics
Subject : Genetics
Lec no : 12
Done By : Mahmoud Al Qusairi
وقل رب زدني علما

3-Post-transcriptional regulation

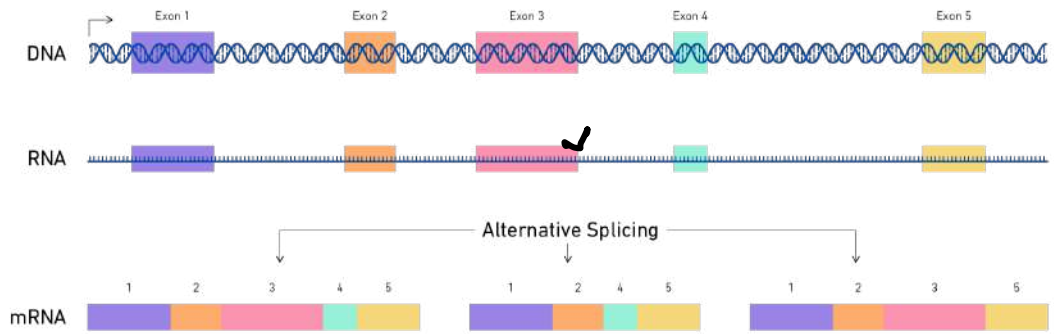
- **Alternative splicing**: for example, in the thyroid gland, the calcitonin gene produces a transcript that codes for the hormone calcitonin , the same gene is expressed in neurons and produces a transcript that codes for calcitonin-related peptide which is involved in taste.



genes ← ليست continuous (بمعنى أنها تحتوي على introns وهي non-coding segments
(translation) انه فقط exons هي التي يحصل لها

- لو حصل transcription لجين معين يحتوي على 5 exons يمكن من خلالها انتاج عدد كبير من الجينات.

- ذكرنا سابقاً أنه كل الخلايا تحمل نفس genetic material
هذا يعني أنه نفس الجين في خلية معينة لنسيج معين
تنتج بروتين معين. ونفس الجين في خلية اخرى
لنسيج آخر تنتج بروتين آخر.



clacitonin gene
- in thyroid gland → produce hormone calcitonin
- in neurons → produce calcitonin-related peptide

❖**Regulation of RNA stability**:

- RNAs have different half-life time e.g. the longer the poly A tail, the longer the half-life time of mRNA.

- Certain proteins interact with mRNA, forming ribonucleoproteins. Some of these proteins protect mRNA from digestion by Rnase enzyme, enhancing translation.

- من ضمن post-transcriptional modifications عملية إضافة poly A tail التي تتحكم في half life time of RNA

كل ما كان poly A tail أطول ← كل ما كان في longer half life time of RNA
← وبالتالي يبقى فترة أطول في cytoplasm ويعمل translational أكثر
← وبالتالي يتم انتاج بروتينات أكثر.

(وتكون stability of RNA أعلى)

- عملية ارتباط بروتينات بـ A tail عملية مهمة ← لأنها تحمي A tail من action of 3' exanucleasis

(poly A binding proteins)

(حيث انه في single strand يأتي exonucleasis ويكسرها)

إلى وبالتالي فإن هذه العملية تعطي stability لـ RNA

❖ mRNA editing:

- The an example known in humans involves the editing of **apolipoprotein B mRNA.**
- Apo B-48 is synthesized by the intestine, and Apo B-100 is synthesized by the liver.
- The apolipoprotein B mRNA synthesized by the intestine is primarily the same as that synthesized by the liver. **However, intestinal cells convert a site-specific cytosine of mRNA to uracil.** This results in the formation of a stop codon near the middle of the mRNA that terminates the synthesis of the growing polypeptide at 48% that of apo B-100.
- The differences in the translated proteins **is not due to alternative splicing but is due to the tissue specific RNA editing event.**

يوجد protein اسمه Apo B protein ويوجد في جسمنا lipoprotein particles (lipid + protein) (كربات عبارة عن دهون ومغلفة ببروتينات) هذه الـ particles لا تستطيع أن تمشي في الدم لأنها water insoluble

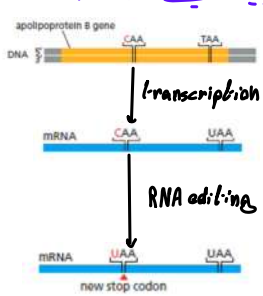
⇓

الحل هو ربطها مع بروتينات وتكون كربات مغلفة ببروتينات من الخارج لأن البروتينات هي water soluble ومن هذه البروتينات التي تغلف هذه particles هي Apo B proteins

- الجين الذي يعطي Apo A protein موجود في كل الخلايا كغيره من الجينات ولكن

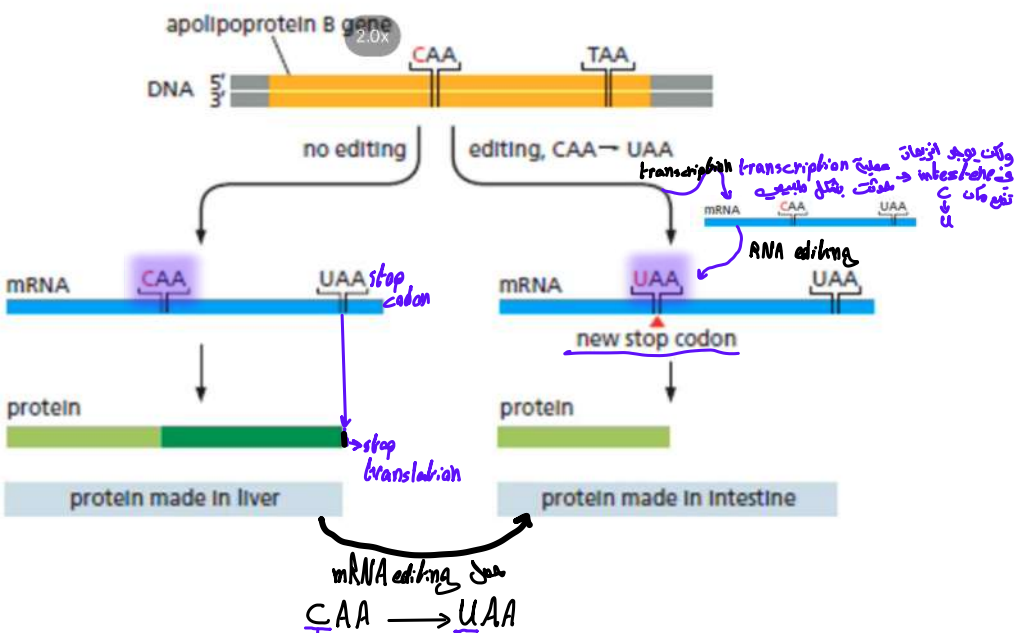
alternative splicing ليست السبب في هذا (هذه عملية مختلفة)

- في intestine ينتج من هذا الجين Apo B 48 لأن هذا البروتين طوله عبارة عن 48% من طول الجين الذي ينتج من نفس الجين في liver



- في liver ينتج من هذا الجين Apo B 100

stop codon = UAA



REGULATION OF GENE EXPRESSION BY NONCODING RNAs

The noncoding RNAs include:

- The rRNA and tRNA molecules, which are responsible for reading the genetic code and synthesizing proteins.
- The RNA molecule in telomerase serves as a template for the replication of chromosome ends
- snRNAs direct RNA splicing.
- **Short RNAs that carry out RNA interference (RNAi)**. Here, short single-stranded RNAs (20–30 nucleotides) serve as guide RNAs that selectively bind—through complementary base-pairing—other RNAs in the cell. When the target is a mature mRNA, the small noncoding RNAs can inhibit its translation or catalyze its rapid destruction. If the target RNA molecule is in the process of being transcribed, the small noncoding RNA can bind to it and direct the formation of repressive chromatin on its attached DNA template to block further transcription

- الجينات سليمة ← عملية transcription تتم بشكل جيد ← تنتج mRNA يحمل modifications
← ولكن يمكن أن تمنع عملية translation (توقف عملية gene expression) عن طريق non coding RNAs

- non coding RNAs لا يوجد عليها codons تتم ترجمتها الى a.a وانتاج منها proteins ولكن لها functions
ملاحظة: tRNA, rRNA هي عبارة عن non coding RNAs حيث انها تمتلك functions ولكن لا يحوي codons (لا تحتوي على) translation لها
translation ← تساعد في عملية

- snRNA هي عبارة عن non coding RNA تدخل في تركيب البروتينات التي تقوم بعملية splicing of exons
← بيعملوا spliceasomes التي تقوم splicing عملية.

- telomerase عبارة عن إنزيم يدخل في تركيبه RNA ولكن ليس له علاقة بعملية translation

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- short RNAs ← عبارة عن single stranded, non coding RNA, قصيرة تتكون من 20 - 30 نيوكليوتايد
← يؤثرون على عملية gene expression عن طريق RNA interference عملية
← يوقفوا عمل mRNA مع العلم أن mRNA سليم (تتعرض عملية translation of mRNA)
← تمسك بـ mRNA يا إما تكسره أو تمنع translation حدوث
mRNA على sequences ل complementire تكون sequences of short RNA

- Three classes of small noncoding RNAs work in this way— ***microRNAs (miRNAs)***, ***small interfering RNAs (siRNAs)***, and ***piwi-interacting RNAs (piRNAs)***. Although they differ in both the way the short pieces of single-stranded RNA are generated and in their ultimate functions, all three types of RNAs locate their targets through RNA–RNA base pairing, and they generally cause reductions in gene expression.

هنالك اكثر من ١٥٠٠ نوع منها
يتم التعبير به فقط ← micro RNAs

interfering RNAs

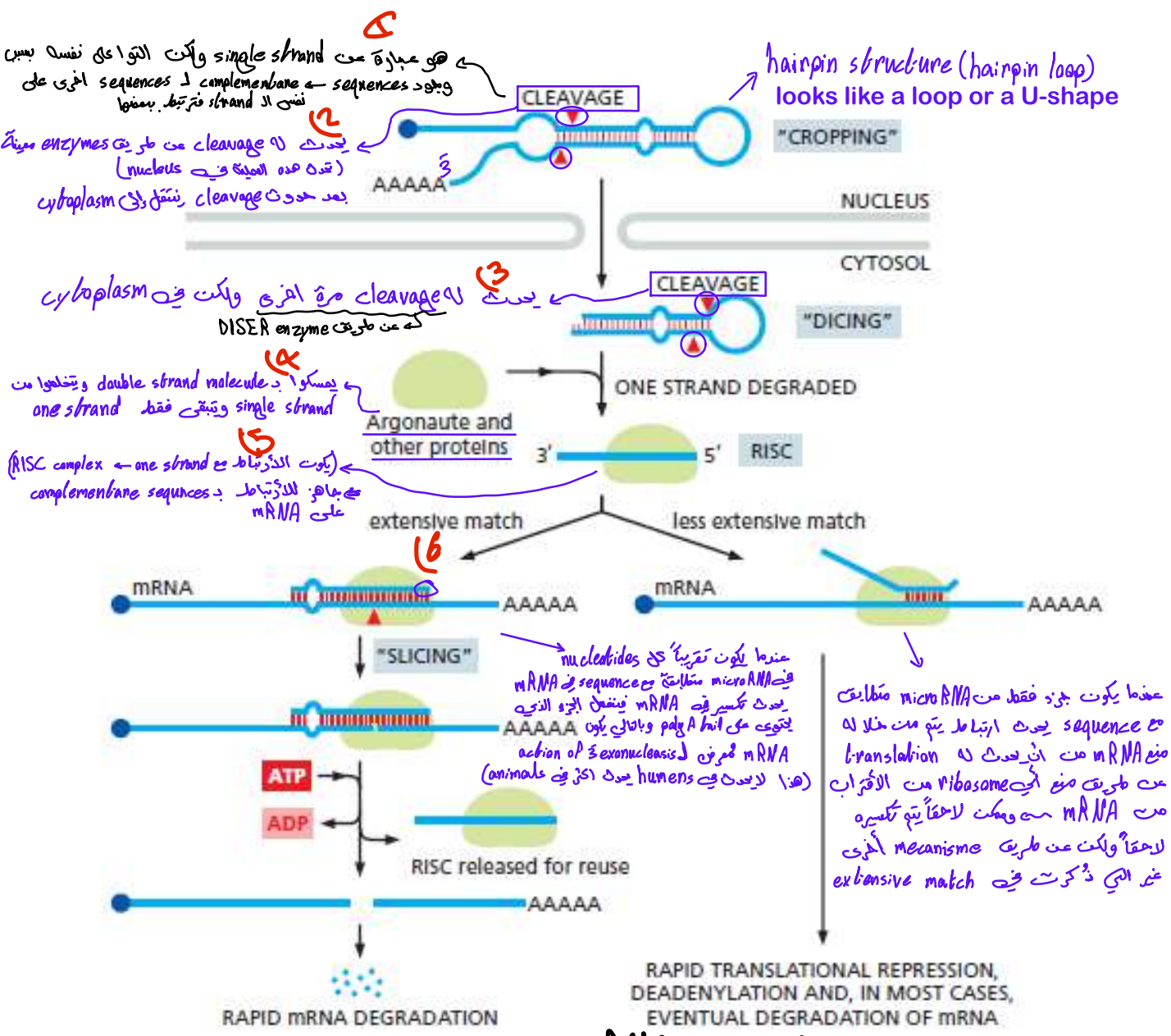
piwi-interacting RNAs

هنالك ٣ أنواع من short RNA تقوم بعملية RNA interference

❖ miRNAs Regulate mRNA Translation and Stability

- More than 1000 different microRNAs (miRNAs) are produced from the human genome. Once made, miRNAs base-pair with specific mRNAs and fine-tune their translation and stability.
- The miRNA precursors are synthesized by **RNA polymerase II** and are **capped** and **polyadenylated**. They then **undergo a special type of processing**, after which the miRNA (typically 23 nucleotides in length) is **assembled with a set of proteins** to form an ***RNA-induced silencing complex, or RISC***. Once formed, the RISC seeks out its target mRNAs by searching for complementary nucleotide sequences

تقاطع مع mRNA ولكن shape مختلف post transcriptional modifications transcription بعد micro RNAs -



The precursor miRNA, through complementary base pairing between one part of its sequence and another, forms a double-strand structure. This RNA is “cropped” while still in the nucleus and then exported to the cytosol, where it is further cleaved (“diced”) by the **Dicer** enzyme to form the miRNA proper.

Argonaute, in conjunction with other components of RISC, initially associates with both strands of the miRNA and then cleaves and discards one of them. The other strand guides RISC to specific mRNAs through base-pairing.

- In animals, the extent of base-pairing is typically at least seven nucleotide pairs, and this pairing most often occurs in the 3′ UTR of the target mRNA. Once an mRNA has been bound by an miRNA, several outcomes are possible.
- **If the base-pairing is extensive** (which is unusual in humans but common in many plants), the mRNA is cleaved (*sliced*) by the Argonaute protein, effectively removing the mRNA's poly-A tail and exposing it to exonucleases.
- After cleavage of the mRNA, the RISC with its associated miRNA is released, and it can seek out additional mRNAs. Thus, a single miRNA can act catalytically to destroy many complementary mRNAs. These miRNAs can thus be thought of as guide sequences that repeatedly bring destructive nucleases into contact with specific mRNAs.

- If the base-pairing between the miRNA and the mRNA is less extensive (as observed for most human miRNAs), Argonaute does not slice the mRNA; rather, translation of the mRNA is repressed by the recruitment of deadenylase enzymes—which shorten the poly-A tail—and other proteins that directly block access of the mRNA to the proteins needed to translate it

❖Q.1 A group of microbiological investigators is studying bacterial DNA replication in E coli colonies. While the cells are actively proliferating, the investigators stop the bacterial cell cycle during S phase and isolate an enzyme involved in DNA replication. An assay of the enzyme,s exonuclease activity determines that it is active on both intact and demethylated thymine nucleotides. Which of the following enzymes have the investigators most likely isolated?

Answer:DNA polymerase |

- DNA ligase
- DNA polymerase III
- Telomerase
- DNA polymerase I
- primase

❖Q.2 An investigator studying DNA replication in campylobacter jejuni inoculates a strain of this organism into a growth medium that contains radiolabeled thymine. After 2 hours, the rate of incorporation of radiolabeled thymine is measured as a proxy for the rate of DNA replication. The cells are then collected by centrifugation and suspended in a new growth medium that contains no new uracil. After another 2 hours, the rate of incorporation of radiolabeled thymine is measured again. The new growth medium directly affects the function of which of the following enzymes?

Answer:primase

- Telomerase
- DNA polymerase I
- DNA polymerase II
- DNA polymerase III
- Ligase
- primase